DESCRIBING AND PREVENTING IMPAIRMENTS IN MENTAL, PHYSICAL AND COGNITIVE HEALTH AMONG SURVIVORS OF CRITICAL ILLNESS

by

Ann M. Parker

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ABSTRACT

Problem: This thesis summarizes the existing literature on early rehabilitation in the intensive care unit (ICU) (Aim 1); conducts two studies evaluating the epidemiology of psychiatric symptoms among survivors of critical illness (2); and evaluates implementation of two different evidence-based interventions (rehabilitation interventions (early mobilization and cognitive stimulation)) as part of usual care to improve ICU-acquired physical and neuropsychological complications (3).

Methods: Aim 1 – Narrative review of the literature on early rehabilitation in the ICU to improve physical and mental health outcomes. 2a –Meta-analysis evaluating posttraumatic stress disorder (PTSD) symptoms in ICU survivors. 2b - Prospective longitudinal cohort study evaluating prevalence and co-occurrence of psychiatric symptoms among acute respiratory distress syndrome (ARDS) survivors. 3a - Pre-post evaluation of the sustainability of structured quality improvement (QI) project focused on early mobilization in medical ICU. 3b – Qualitative evaluation of barriers and facilitators to implementing cognitive stimulation, as part of a usual care, in an ICU.

Results: Aim 1 - Early rehabilitation interventions targeting physical impairments in the ICU may be effective. 2a – The search identified 28 articles (3,428 patients). Between 1-6 months post-ICU (6 studies; n=456), the pooled prevalence of clinically important PTSD symptoms [95% CI] was 25% [18-34%]. 2b - During 12 months, 416 (66%) of 629 patients with ≥1 psychiatric outcome measure had substantial symptoms in ≥1 domain. The most common pattern of co-occurrence was having symptoms of all 3 psychiatric domains. 3a - More patients post-QI versus pre-QI were able to stand/transfer/ambulate in the ICU (64% vs. 7%, p<0.001). Among post-QI versus pre-QI patients, there was a shorter median [IQR] time to first physical therapy (4 [2,6] vs. 11 days [6,29], p<0.001), which was sustained over the 5 years during the post-QI period. 3b - Twenty-three MICU nurses identified 12 barrier and 9 facilitator themes corresponding to the each of the Consolidated Framework for

Implementation Research domains. Patient-specific variables (e.g. sedation) were most frequently reported.

Conclusions: Impairments in mental health and physical function are common among survivors of critical illness. The use of structured quality improvement processes can contribute to sustained implementation of evidence-based interventions in the ICU.

Dissertation Readers: Dale M. Needham, MD, PhD; Franklin Adkinson, MD; O. Joseph Bienvenu, MD, PhD; Marie Diener-West, PhD

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CHAPTER 1: INTRODUCTION

As the population ages, a growing number of Americans are requiring critical care, including mechanical ventilation for acute respiratory failure.[1] At the same time, improvements in the management of critically ill patients have resulted in decreased mortality.[2] Hence, there is a growing population of survivors of critical illness who experience long-term complications in physical function, mental health, and cognition. Collectively, these impairments are termed the "Post-Intensive Care Syndrome" (PICS).[3]

Post-Intensive Care Syndrome

These impairments in physical, cognitive, and mental health status are associated with worse health-related quality of life and can persist for years after discharge from the intensive care unit (ICU).[3,4] Prolonged bedrest and immobilization during critically illness can lead to neuromuscular weakness and impaired physical function.[5] More than half of survivors of critical illness will have impairments in activities of daily living (ADLs) at one year after discharge, while among those who require mechanical ventilation, nearly 70% will have substantial impairments in ADLs.[6,7] Moreover, studies evaluating patients who were relatively young and had few pre-ICU comorbidities reported that 50% had not returned to work at a year post-ICU discharge, and the majority reported muscle weakness as a major contributor to their inability to return to work.[5,8]

Survivors of critical illness similarly experience substantial impairments in mental health, including depression, anxiety and posttraumatic stress disorder (PTSD) symptoms. Approximately one-third of critical illness survivors will experience substantial depressive symptoms over the year following discharge from the ICU,[9] with a similar number being affected by anxiety symptoms.[10] In a prospective, longitudinal study of acute respiratory failure survivors, one-third developed PTSD symptoms over the two years following ICU discharge.[11]

Finally, survivors of critical illness also have considerable impairments in cognition that persist well beyond the acute hospitalization. In a study of 821 critically ill patients, 75% of whom were delirious during the hospital stay, one-third had scores on cognitive testing that were consistent with moderate traumatic brain injury while one quarter had scores consistent with mild Alzheimer's Disease at one year follow-up.[12] Notably, this cognitive impairment affected not just older, more vulnerable patients, but young patients as well. Importantly, a longer duration of delirium in the ICU was associated with worse cognitive impairment at one-year follow-up.[12]

There are currently few evidence-based methods for the prevention or treatment of long-term complications after critical illness. Notably, early mobilization and physical rehabilitation in the first 48 hours of admission to the intensive care unit has been associated with improved strength, physical function and quality of life.[13-15] Similarly, cognitive stimulation in the intensive care unit has been shown to decrease the incidence and duration of delirium, which is an important risk factor for long-term cognitive impairment.[16,17]

Thesis Aims

This thesis aims to evaluate the prevalence of, and risk factors for, complications of critical illness and to evaluate interventions focused on preventing and treating such impairments, as follows:

1) Synthesize the existing literature on early rehabilitation in the intensive care unit with a goal of reducing physical and mental health impairments in survivors. (Parker et al., Curr Phys Med Rehabil Reports. 2013)

2) Describe the prevalence of psychiatric symptoms in survivors of critical illness, via the following:

a. Determine the prevalence of PTSD symptoms after critical illness and summarize associated risk factors via a systematic review and meta-analysis of the existing literature. (Parker et al., CCM, 2015)
b. Evaluate the prevalence and co-occurrence of, and risk factors for, depression, anxiety and PTSD symptoms in the year following acute respiratory distress syndrome. (Huang, M., Parker, AM, et al., CCM, 2016)

3) Evaluate the implementation, in routine clinical practice, of evidence-based interventions designed to reduce immobility and delirium in the intensive care unit, as follows:
    a. Evaluate the sustained effect of a quality improvement project on the early initiation of physical therapy interventions in the intensive care unit. (Dinglas VD & Parker AM (co-first authors), et al., Annals ATS, 2014)
    b. To understand perceived barriers to implementing a cognitive stimulation intervention via qualitative research methods t. (Parker et al, under review)

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CHAPTER 2:

Early Rehabilitation in the Intensive Care Unit:

Preventing Physical and Mental Health Impairments

Ann Parker, MD[1,2], Thiti Sricharoenchai, MD[1,2,4] and Dale M. Needham, FCA, MD, PhD[1,2,3]

1Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine
2Outcomes After Critical Illness and Surgery (OACIS) Group, Johns Hopkins University
3Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine
4Division of Pulmonary and Critical Care Medicine, Thammasat University, Pathum Thani, Thailand;

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Abstract

Survivors of critical illness often experience new or worsening impairments in physical, cognitive and/or mental health, referred to as post-intensive care syndrome (PICS). Such impairments can be long-lasting and negatively impact survivors' quality of life. Early rehabilitation in the intensive care unit (ICU), while patients remain on life-support therapies, may reduce the complications associated with PICS. This article addresses evidence-based rehabilitation interventions to reduce the physical and mental health impairments associated with PICS. Implementation of effective early rehabilitation interventions targeting physical impairments requires consideration of 5 factors: barriers, benefits, feasibility, safety, and resources. Mental health impairments may be addressed by the following interventions: ICU diaries, early in-ICU psychological intervention, and post-ICU coping skills training. In both cases, a multidisciplinary team-based approach is paramount to the successful incorporation of early rehabilitation into routine practice in the ICU.

Introduction

The term Post-Intensive Care Syndrome (PICS) refers to new or worsening impairments in physical, cognitive and/or mental health in ICU survivors [1]. These morbidities persist beyond the acute care hospitalization and can be long-lasting, negatively impacting quality of life [1-3]. This review focuses on new research evaluating evidence-based rehabilitation interventions to reduce the physical and mental health impairments associated with PICS.

Critically ill patients are often exposed to prolonged immobilization, which can lead to neuromuscular weakness and subsequent impairments in physical function lasting for months to years after discharge from the intensive care unit (ICU) [4-6]. For instance, almost all ICU survivors have decrements in performing activities of daily living a year after discharge, and neuromuscular abnormalities persist for up to 5 years in 84% to 95% of ICU survivors with critical illness polyneuropathy [2, 5]. Additionally, survivors of critical illness are at risk for mental health problems, including anxiety, depression and post-traumatic stress disorder (PTSD) [7-10]. The median prevalence for clinically important anxiety and depression symptoms in ICU survivors is 24% and 28%, respectively [7, 11], and one-third of patients develop PTSD symptoms in the first 2 years following critical illness [12].

Early rehabilitation is essential to reducing complications associated with PICS [1, 13-15]. “Early” refers to rehabilitation interventions that commence immediately after stabilization of physiologic derangements, often while patients remain on mechanical ventilation and vasopressor infusions [1, 15-18]. A shift in ICU “culture” with a focus on interventions to reduce subsequent physical and mental health impairments is essential to successful implementation of an early rehabilitation program [19, 20].

Early Rehabilitation for Neuromuscular Weakness

Implementation of an early rehabilitation program, incorporating physical and occupational therapy, requires consideration of potential barriers, feasibility, benefits to be achieved, safety, and necessary resources, as described below [16]. Further information and support for ICU-based rehabilitation can be found via an international Mobilization Network **(**www.mobilization-network.org).

Potential Barriers to Rehabilitation in the Critically Ill patients

Inadequate multidisciplinary staffing and collaboration, deep sedation and a lack of knowledge regarding benefits to patients are among the most important potential barriers to successful implementation of early rehabilitation programs [20-24]. In a prospective observational study in the ICU, rehabilitation therapy was not provided for a median [Interquartile Range (IQR)] of 56% [25%-68%] of ICU days per patient due to limited availability of rehabilitation staff [22]. A subsequent quality improvement project at Johns Hopkins Hospital, including dedication of a full-time physical therapist and occupational therapist to this ICU, resulted in an increase in rehabilitation sessions and improved physical function among mechanically ventilated patients [25]. This quality improvement project also incorporated multidisciplinary education for all members of the ICU and rehabilitation team to address potential gaps in knowledge.

Deep sedation can also limit patient participation in early rehabilitation [20, 22, 25]. The observational pilot study, mentioned above, reported that mechanically ventilated patients were ineligible for rehabilitation therapy for a median [IQR] of 27% [15%-61%] of ICU days per patient due to sedation and/or non-responsiveness [22]. In a pre-post study of 104 patients requiring mechanical ventilation > 4 days, the absence of sedatives was predictive of increased ambulation (OR 1.90; 95% CI 1.19-3.15, p=0.009) [19]. Moreover, analyses of a prospective cohort of >500 patients revealed that continuous

sedative infusion was associated with longer time to first physical and first occupational therapy sessions [23, 26]. Evidence-based protocols to limit sedation and facilitate weaning from mechanical ventilation [27-30] are advocated to assist with early rehabilitation [31].

Feasibility

An ICU "culture" supporting quality improvement and evidence-based rehabilitation interventions is essential to a successful early rehabilitation program [16, 20]. In addition to the barriers mentioned above, rehabilitation therapy in the ICU can be limited by patient availability due to diagnostic testing and therapeutic procedures. Multidisciplinary collaboration may help ensure patient availability, adequate staffing and the coordination needed to achieve early rehabilitation in the busy ICU environment. As described below, such collaboration may be solidified through development of ICU-specific protocols and order-sets to enhance the delivery of early rehabilitation programs [29, 32, 33].

A pre-post study of patients mechanically ventilated > 4 days demonstrated that intra-hospital transfer from a traditional ICU to a Respiratory ICU, where active mobilization is a priority, was associated with increased patient ambulation [20] (odds ratio (OR) 2.47, $p<0.001$) [19]. This change was not explained by improved physiologic status, but attributed to the "culture" and multidisciplinary focus on early mobilization in the Respiratory ICU. Nursing and rehabilitation staffing was identical between the traditional ICU and Respiratory ICU, demonstrating the value of a collaborative "culture" supporting rehabilitation practices. This "culture of mobility" promotes prioritization of early rehabilitation as routine care for the eligible patients through multidisciplinary education and engagement [34].

Protocols and order sets may improve the effectiveness of an early rehabilitation program. In a prospective trial, 330 patients were assigned to either usual care or early physical therapy delivered

according to a protocol by an ICU Mobility Team, consisting of a critical care nurse, physical therapist, and nursing assistant [35]. The mobility protocol included an automatic physician order for physical therapy rather than a physician-determined manual order. A greater proportion of patients in the protocol versus usual care group participated in at least one physical therapy session during their hospital stay (80% versus 47%, $p \leq 0.001$). Of those receiving physical therapy, more patients in the protocol versus usual care group had treatment initiated while in the ICU (91% versus 13%, $p \leq 0.001$).

The usefulness of a nurse-driven mobility protocol and computerized order set was evaluated in a pre-post evaluation including ICU and intermediate care patients [32]. The proportion of ICU and intermediate care patients ambulating within 72 hours of admission increased by 14% and 56%, respectively, after the protocol was initiated ($p<0.001$). Moreover, a quality-improvement project including 100 consecutive patients in a surgical ICU (SICU) evaluated the mandatory entry of computerized mobility orders as well as a mobility protocol for nurses [33]. The protocol included physiologic criteria for patient screening with re-evaluation of ineligible patients every 6 hours until eligible or transferred out of the unit. The proportion of patients with mobility orders and mobilized increased after the intervention (82% versus 58%, $p<0.05$ and 80% versus 22%, $p<0.05$, respectively). Finally, a clinical trial involving 193 patients assigned to either usual care or protocol-driven physiotherapy in a SICU reported a greater proportion of therapy sessions involved mobility in the protocol versus usual care group (82% versus 66%, $p<0.001$) [36]. Thus, a change in “culture”, enhanced by the addition of computerized order sets and mobility protocols, may result in greater mobility among ICU patients.

Benefits

Potential benefits for patients participating in early rehabilitation in the ICU include improved muscle strength, physical function and quality of life [6, 13, 14, 37]. Additionally, early rehabilitation programs may be associated with reduced hospital and ICU length of stay (LOS), duration of mechanical ventilation and hospital costs [6, 13, 14, 25, 37, 38].

Muscle Strength, Physical Function, and Quality of Life

Early rehabilitation is associated with improved muscle strength, physical function and quality of life in ICU survivors. In three systematic reviews [13, 14, 37], ICU-based rehabilitation was associated with earlier achievement of mobility milestones[15, 19, 25, 35] and improved muscle strength [39, 40] including measures of respiratory, upper limb and/or lower limb strength. In one randomized controlled trial (RCT), supine cycle ergometry in mechanically ventilated patients was associated with improved physical function and quality of life [39].

In an RCT of early physical and occupational therapy in 104 mechanically ventilated patients, ICU-acquired weakness, as evaluated by manual muscle strength testing, occurred in 31% versus 49% of patients in the intervention versus control group (p=0.09) [15]. Additionally, the greatest unassisted walking distance at hospital discharge was longer in the intervention versus control group (median [IQR] 33m [0-91m] versus 0m [0-30m], p=0.004). Finally, independent functional status at hospital discharge (the trial's primary outcome) was achieved by a greater proportion of patients in the intervention group (59% versus 35%, p=0.02).

Implementation of early rehabilitation, as a part of routine care in the ICU, has also demonstrated improved physical function. In a prospective observational evaluation involving 104 patients requiring mechanical ventilation >4 days in a Respiratory ICU, the average distance ambulated on the last day of

ICU stay was 238 feet, which is much greater than otherwise expected [19]. Likewise, a prospective quality improvement project was associated with an increase in the proportion of patients receiving rehabilitation interventions having a functional mobility level of sitting or greater (56% pre-intervention versus 78% post-intervention, p=0.03) [25].

Reduced Duration of Mechanical Ventilation, Length of Stay (LOS) and Costs

Early rehabilitation may be associated with reduced healthcare costs resulting from a reduction in duration of mechanical ventilation, and ICU and hospital LOS [35, 37, 41, 42]. A significant reduction in the duration of mechanical ventilation has been reported in three studies [15, 40, 43]. One of these studies, an RCT of early physical and occupational therapy versus usual care, demonstrated a reduced median (IQR) duration of mechanical ventilation of 3.4 [2.3-7.3] versus 6.1 [4.0-9.6] days (p=0.02), and a reduced median (IQR) ICU LOS (5.9 [4.5–13.2] versus 7.9 [6.1–12.9] days, p=0.08) [15].

A medical ICU (MICU) quality improvement project, consisting of a multidisciplinary team approach to sedation and rehabilitation practices, was associated with a decrease in average ICU and hospital LOS of 2.1 and 3.1 days, respectively, with a 20% increase in MICU admissions compared with the same period from the prior year [25].

In a prospective trial of 330 MICU patients, early rehabilitation with a mobility protocol versus usual care was associated with a shorter adjusted ICU and hospital LOS (mean 5.5 versus 6.9 days, p=0.025 and 11 versus 15 days, p=0.006, respectively) [35]. Moreover, the mean cost per patient was lower in the protocol versus usual care group ($41,142 versus $44,302). Total costs were also reduced in the protocol versus usual care group, even after accounting for the additional cost associated with implementing the mobility team for the intervention group ($6,805,082 versus $7,309,871).

A financial model, based on outcomes associated with implementation of an early rehabilitation program in the Johns Hopkins MICU as well as existing publications, projected a net financial savings in 20 (83%) of 24 different scenarios with financial estimates ranging from $88,000 (net cost) to $3,763,000 (net savings) from investment in an early rehabilitation program [42].

Safety

Clinical trials as well as studies of routine clinical care have verified the safety of early rehabilitation in critically ill patients. In two systematic reviews, no serious adverse events resulting in death or near-death were reported, with the most common potential adverse event being a transient decrease in oxygen saturation [13, 14]. Inadvertent removal of endotracheal tubes, vascular catheters or other support devices was rare.

Observational Studies with Safety Data

A prospective study of 31 patients participating in 69 mobilization sessions in a single ICU described the physiologic consequences of mobilizing critically ill patients [44]. The proportion of patients mechanically ventilated with a tracheostomy was 23% (7/31), and the remaining 24 patients were not mechanically ventilated. Activity levels consisted of sitting on the edge of the bed with progression to standing in place, transferring to a chair or ambulating. Heart rate and blood pressure significantly increased during rehabilitation interventions while there was a non-significant decrease in oxygen saturation. In only 3 of 69 sessions (4%), there was a decrease in oxygen saturation requiring a temporary increase in FiO2. Otherwise, no potential safety events required additional therapy, and no life-threatening adverse events occurred despite most of the sessions (91%) involving patients with limited cardiopulmonary reserve prior to mobilization. Similar findings were reported in a prospective

observational pilot study of early rehabilitation involving 19 mechanically ventilated patients in the Johns Hopkins MICU, in which heart rate, oxygen saturation, and blood pressure were monitored and recorded during 50 rehabilitation sessions [22]. There were only small and clinically inconsequential changes in these physiologic parameters.

In a prospective, observational evaluation of 1,449 early rehabilitation activities in 103 patients requiring mechanical ventilation >4 days in a Respiratory ICU, adverse events were rare, occurring in only 14 (<1%) activities [17]. Patients with an endotracheal tube participated in 593(41%) activity events, which ranged from sitting on the edge of a bed to ambulating. Potential safety events, which included fall (5 occasions), systolic blood pressure <90 mmHg (4 occasions) or >200 mmHg (1 occasion), oxygen saturation <80% (3 occasions), and feeding tube removal (1 occasion), did not result in any additional therapy, LOS or healthcare costs.

Clinical Trials with Safety Data

Four clinical trials demonstrated the safety of early rehabilitation interventions in critically ill patients [15, 35, 36, 39]. In an RCT occurring in one MICU and one SICU at a single center, 90 patients were randomized to either standard rehabilitation therapy alone or standard therapy plus active training with a bedside lower extremity cycle ergometer [39]. Of the 90 patients, 84% were on mechanical ventilation at the time of trial enrollment. Physiologic changes prompted the cessation of activity in only 16 (4%) of 425 sessions with the cycle ergometer, with resolution occurring within 2 minutes. There was one Achilles tendon rupture associated with cycling.

In another RCT, 104 patients on mechanical ventilation via an endotracheal tube in 2 MICUs were assigned to either usual care or early physical and occupational therapy [15]. Serious adverse events,

defined as fall to knees, endotracheal tube removal, systolic blood pressure >200 or <90 mm Hg, and desaturation to <80%, occurred in only 1 of 498 (0.2%) sessions. This single event was oxygen desaturation. Physiologic derangements, most commonly perceived patient-ventilator asynchrony, resulted in the premature discontinuation of therapy in only 4% of all sessions. Inadvertent removal of tubes and lines was also recorded, revealing the removal of a single radial arterial catheter. No falls or unplanned endotracheal tube removal were reported.

In another trial, 330 patients mechanically ventilated via an endotracheal tube were assigned to either usual care or protocol-driven early physical therapy with an ICU Mobility Team [35]. Of the 145 patients assigned to the intervention group, 73% participated in at least one physical therapy session while in the ICU. There were no deaths, near-deaths or cardiopulmonary resuscitation during physical therapy sessions. There were no potential safety events such as accidental removal of a device. Patient fatigue was the most common reason for ending a mobility session, without any clinically important change in physiologic parameters.

In a fourth trial, 163 patients in a SICU received physical therapy according to usual care or a physiotherapy protocol [36]. Protocol patients participated in a total of 615 treatment sessions, with 5 adverse events occurring in 4 sessions. These events included hemodynamic instability (2 events), unintentional removal of a peripheral intravenous catheter (2 events), and fall to knees (1 event).

Rehabilitation with Central Venous and Arterial Catheters

Several studies have demonstrated the safety of early rehabilitation in patients with central venous and arterial catheters [18, 45, 46]. In a retrospective case-series, 30 patients in a cardiovascular ICU (CVICU) participated in 156 activity events ranging from sitting to walking with a femoral arterial catheter in

place, with no catheter-related adverse events occurring as a result of physical therapy [45]. In a prospective study, 77 CVICU patients with a femoral catheter participated in 210 physical therapy sessions encompassing 630 mobility activities [47]. The following catheter-related events were evaluated: bleeding, hematoma, line dislodgement, nonfunctioning catheter or a change in vascular status, with no events (0% event rate) occurring during or immediately after any mobility activity.

Another evaluation of 49 MICU patients participating in 183 physical therapy sessions while on mechanical ventilation with a central venous and 115 sessions with an arterial catheter in place, reported inadvertent removal of only 1 arterial and 0 central venous catheters [18]. In this study, the internal jugular vein was the most common venous catheter site (43% of catheter-days), followed by subclavian (29%) and femoral (10%) veins, and in 47% of sessions, an arterial catheter was present. Of all sessions taking place, continuous hemodialysis and at least one vasopressor infusion was present during 9% and 17%, respectively. Similarly, in a prospective study of 109 patients receiving continuous hemodialysis, 104 (95%) underwent mobility within 48 hours of starting continuous hemodialysis [48]. There were no life-threatening events associated with mobility, and the only potential safety event was one temporary disconnection from the circuit. Patients with jugular and femoral access participated in mobility, but patients with jugular access were more likely to progress to more advanced mobility interventions.

A larger prospective evaluation conducted in the Johns Hopkins MICU evaluated 101 consecutive patients who underwent 253 physical therapy sessions with a femoral catheter *in situ*, most commonly venous catheters, which accounted for 71% of patient days with physical therapy [46]. No femoral catheter-related adverse events occurred during rehabilitation activities (event rate: 0%; upper 95% confidence bound: 1.4%). Femoral catheter-related events were defined as: non-functioning catheter,

removal of catheter, bleeding at catheter site, catheter line-associated blood stream infection, retroperitoneal hematoma, and limb ischemia. The highest activity levels in physical therapy sessions conducted with a femoral catheter *in situ* were in-bed exercises (38%), sitting (27%), standing/walking (23%), and supine cycle ergometry (12%).

Screening for Patient Safety

Clinical judgment to assess patient appropriateness for active mobilization is important for safely implementing an early rehabilitation program in the ICU. Multidisciplinary collaboration can augment the decision-making process. An algorithm can be useful to screen patients for stability prior to initiation of physical or occupational therapy interventions [16, 44].

Resources for Early Rehabilitation in the ICU

General Resources

Contributions from all members of the multidisciplinary team are important for the successful implementation of early rehabilitation in an ICU [16, 20, 23, 25]. Additionally, a medical director may advocate for the appropriate allocation of staff, resources and equipment to ensure that all eligible patients are able to safely engage in rehabilitation activities [25].

Critically ill patients are often tethered to various medical devices via lines and tubes, making mobilization, and especially ambulation, challenging. Trained staff and assistive equipment can improve the safety and efficiency of ambulating critically ill patients [16]. A rolling IV pole allows transport of infusing medications. Additionally, ambulating with mechanically ventilated patients necessitates either a battery-powered standard ventilator, portable ventilator or Ambu bag with an oxygen source. Finally, patients may require use of a walker and wheelchair for support and for a seated rest break. Moreover,

cardiac and oxygen saturation monitors are generally used. A mobility aid, which consolidates all of the necessary equipment into one portable device, has been used in the Johns Hopkins MICU and elsewhere to help simplify patient ambulation and reduce staffing needs [32, 49].

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) induces passive muscle contraction in targeted muscle groups via skin electrodes. Several Phase II clinical trials of NMES in ICU populations show favorable initial results. One clinical trial, which randomly assigned 46 patients mechanically ventilated <7 days or >2 weeks to NMES versus sham, found that patients on mechanical ventilation >2 weeks who received NMES had a greater improvement in quadriceps muscle thickness (+4.9% versus -3.2%, p=0.013) [50]. In another clinical trial of 140 critically ill, mostly (97%) requiring mechanical ventilation, daily NMES versus usual care was associated with a lower incidence of ICU-acquired weakness in the 52 patients who could be evaluated for this outcome (13% versus 39%, p=0.04) [40]. Conflicting results were presented by two small RCTs of patients with septic shock, in which NMES was applied to one leg of each patient with the contralateral limb serving as a control. In the first trial, involving 8 patients, the quadriceps muscle volume between groups was similar at 7 days [51]. In the other trial, 16 patients were randomized for 13 days, and quadriceps and biceps strength were greater in the group receiving NMES at 13 days (p=0.034 and p=0.005 respectively) [52]. Patients with greater baseline weakness showed the most improvement.

Cycle Ergometer

A bedside ergometer is a stationary cycling device that allows for passive or active cycling with increasing levels of resistance. In an RCT of 90 critically ill patients, those assigned to standard physical therapy plus cycling exercises versus standard therapy alone demonstrated greater improvement in muscle strength, physical function, and quality of life at hospital discharge [39]. Patients in the

intervention group cycled passively (if sedated or nonresponsive) or actively 20 minutes per day, five days per week. In the intervention group, the proportion of patients actively cycling increased from 45% to 87% from the first to the final cycling session before ICU discharge. At hospital discharge, patients in the intervention versus control group had a greater 6 minute walk distance (median [IQR] 196m [126–329m] versus 143m [37–226m], $p<0.05$), quadriceps muscle force (2.4±0.6N·kg^{-1}versus 2.0± 0.8N·kg^{-1}, $p<0.05$) and quality of life, (SF-36 Physical Function domain score: median [IQR] 21 [18–23] versus 15 [14–23], $p<0.01$).

Early Rehabilitation for Mental Health Impairments

Interventions to reduce the mental health impairments associated with PICS have received relatively less research than interventions focusing on the physical aspects of recovery. However, there are three interventions that show promising results: ICU diaries, early in-ICU psychological intervention, and out-patient telephone-based coping skills intervention [53-56].

ICU Diaries

Three studies, including two RCTs, support the use of ICU diaries to reduce mental health complications, such as anxiety, depression and PTSD in ICU survivors [54, 55, 57]. In one multicenter RCT conducted in 12 ICUs at 6 general district hospitals and 6 university hospitals, medical staff and family kept a daily diary, including both pictures and text, for each patient during the ICU stay [55]. At one month follow-up after ICU discharge, 352 patients who were mechanically ventilated while in the ICU were randomized to receive their diaries as soon as desired (intervention) versus at 3 months (control). In the intervention group, 87% of patients received their diary at randomization, with the remainder receiving the diary within the following month. Intervention group patients reported reading the diary a median [IQR] of 3 times [0-20]. At 3 month follow-up, fewer patients in the intervention versus control group had new-

onset PTSD (5% versus 13%, p=0.02), with patients having the greatest PTSD symptoms at 1 month having the greatest benefit of the diary intervention. Another RCT evaluated 36 patients in a single medical-surgical ICU [54]. Patients were assessed for symptoms of anxiety and depression on average 1 month post-ICU discharge and 3 weeks later. Patients in the intervention group received their ICU diary at the first assessment. Anxiety and depression symptoms decreased significantly ($p<0.05$ and $p<0.005$, respectively) in the intervention group from the first assessment to the second, while scores remained the same in the control group.

A prospective pre-post trial evaluated mental health symptoms at 3 and 12 month follow-up in 143 patients who were assigned to either an ICU diary group or control group [58]. A total of 49 patients were assigned to the intervention group and received their diary at hospital discharge. At 3 month follow-up, there was no significant difference between groups with regard to anxiety and depression, but at 12 months, patients in the intervention versus control group had less PTSD symptoms (Impact of Events Scale – Revised score: mean (SD) 32.1 (15.4) versus 21.0 (12.2), p=0.004). Hence, clinical research supports the use of simple and inexpensive ICU diaries to reduce mental health complications associated with ICU survivorship. An international ICU Diary Network (www.icu-diary.org) is available to assist and support use of ICU diaries.

Early In-ICU Psychological Intervention

A pre-post study of 209 patients admitted to a trauma ICU in Italy evaluated the mental health outcomes, at 12 month follow-up, of an in-ICU psychological intervention (delivered as part of routine care - the "post" period) versus usual care that did not include a psychologist in the ICU (the "pre" period) [53]. In the post- versus pre-psychologist period, the proportion of patients with clinically important PTSD symptoms at 12 months after ICU discharge was lower (21% versus 57%, p<0.001), with

similar non-significant trends observed for anxiety and depression symptoms (9% versus 17%, p=0.088 and 7% versus 13%, p=0.145, respectively). In this study, the psychologist performed a range of interventions in the ICU, including providing education, counseling, stress management, psychological support and coping strategies.

Post-discharge Coping Skills Intervention

Adaptive coping skills training is an evidence-based method for reducing symptoms of anxiety and PTSD in non-ICU patient populations [59, 60], and there is interest in evaluating this intervention in ICU patients [56]. One prospective pilot study (n=7) evaluated the association between a 12 session post-discharge, telephone-based coping skills intervention and mental health symptoms in acute respiratory distress syndrome survivors [56]. The number of patients with clinically important PTSD symptoms decreased from 5 patients at enrollment to 1 patient after the intervention was complete. Additionally, depression and anxiety symptoms decreased following the intervention (Hospital Anxiety and Depression (HAD) sub-scale scores: depression 11.2 versus 7.3, and anxiety 12.2 versus 6.2). Further research is needed to clarify the role of coping skills in mental health recovery for ICU survivors.

Conclusion

Early rehabilitation interventions in the ICU may reduce physical and mental health complications frequently occurring in survivors of critical illness. Potential benefits associated with early physical rehabilitation include improved muscle strength, physical function and quality of life, as well as reduced healthcare costs and LOS. Such ICU-based rehabilitation interventions are safe and feasible when conducted in the context of a multidisciplinary team approach. ICU diaries, along with other ICU-based and out-patient psychological interventions, are worthy of consideration as means of reducing the burden of mental health complications after critical illness. Ongoing evaluation and implementation of

early rehabilitation programs for critically ill patients should be considered to address the common and long-lasting impairments associated with post-intensive care syndrome.

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CHAPTER 3:

SECTION A:

Posttraumatic Stress Disorder in Critical Illness Survivors: A Meta-analysis

Ann M. Parker, MD[1,2], Thiti Sricharoenchai, MD[3], Sandeep Raparla, MD[4], Kyle W. Schneck, BA[5], O. Joseph Bienvenu, MD, PhD[2,6], and Dale M. Needham, FCA, MD, PhD[1,2,7]

[1]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine
[2]Outcomes After Critical Illness and Surgery (OACIS) Group, Johns Hopkins University
[3]Division of Pulmonary and Critical Care Medicine, Thammasat University, Pathum Thani, Thailand
[4]Department of Internal Medicine, Good Samaritan Hospital
[5]Department of Linguistics and Cognitive Science, University of Delaware
[6]Department of Psychiatry, Johns Hopkins University School of Medicine
[7]Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine

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Abstract

OBJECTIVE: To conduct a systematic review and meta-analysis of the prevalence, risk factors, and prevention/treatment strategies for post-traumatic stress disorder (PTSD) symptoms in critical illness survivors.

DATA SOURCES: PubMed, Embase, CINAHL, Psyc INFO, and Cochrane Library from inception through March 5, 2014

STUDY SELECTION: Eligible studies met the following criteria: (1) adult general/non-specialty ICU, (2) validated PTSD instrument ≥1 month post-ICU, and (3) sample size ≥10 patients.

DATA EXTRACTION: Duplicate independent review and data abstraction from all eligible titles/abstracts/full-text articles

DATA SYNTHESIS: The search identified 3,243 titles/abstracts, with 28 eligible articles on 25 unique cohorts (n=3,428 patients). The Impact of Events Scale (IES) was the most common PTSD instrument. Between 1-6 months post-ICU (6 studies; n=456), the pooled mean [95% CI] IES score was 20 [17-24], and the pooled prevalences of clinically important PTSD symptoms [95% CI] were 25% [18-34%] and 44% [36-52%] using IES thresholds ≥35 and ≥20, respectively. Between 7-12 months post-ICU (5 studies; n=698), the pooled mean IES score was 17 [9-24], and pooled prevalences of PTSD symptoms were 17% [10-26%] and 34% [22-50%], respectively. ICU risk factors for PTSD symptoms included benzodiazepine administration, mechanical ventilation, and post-ICU memories of frightening ICU experiences. PTSD symptoms were associated with worse quality of life. In European-based studies: (1) an ICU diary was associated with a significant reduction in PTSD symptoms, (2) a self-help rehabilitation manual was associated with significant PTSD symptom reduction at 2 months, but not 6 months; and (3) a nurse-led ICU follow-up clinic did not reduce PTSD symptoms.

CONCLUSIONS: Clinically important PTSD symptoms occurred in 1/4 of critical illness survivors at 1-year follow-up, with higher prevalence in those who had comorbid psychopathology, received

benzodiazepines, and had early memories of frightening ICU experiences. In European studies, ICU diaries reduced PTSD symptoms.

Introduction

As mortality from critical illness decreases, there is an ever-growing population of critical illness survivors who frequently experience long-lasting physical, cognitive and mental health impairments.[1-5] Posttraumatic stress disorder (PTSD) is one important mental health impairment related to life-threatening ICU experiences. According to the Diagnostic and Statistical Manual of Mental Disorders 5, PTSD can be diagnosed if an individual is exposed to actual or threatened serious injury/death (e.g. critical illness and related intensive care unit (ICU) treatments) and subsequently develops the following symptoms which last >1 month and cause significant distress or changes in functionality: persistently re-experiencing the event and attempting to avoid trauma-related stimuli; new negative alterations in mood/cognition; and new/increased arousal/reactivity. Prior systematic reviews reported substantial PTSD symptoms occurred in 5 to 63% of critical illness survivors and were associated with worse health-related quality of life.[6-9] Previously described risk factors for PTSD include younger age, sedation with benzodiazepines, and recall of frightening ICU experiences.[6-8] PTSD in the general population is associated with greater physical disability.[10-12]

The burden of PTSD symptoms in critical illness survivors has gained increasing recognition in the past 5 years, with the number of studies published on this topic more than doubling compared with the preceding 5 year interval.[7] Moreover, there is increasing homogeneity between studies regarding the instruments used for and timing of PTSD symptom assessment post-ICU. Such consistencies in study design provide new opportunities for pooling data on prevalence and severity of PTSD symptoms across studies. In addition, over the past 5 years, evidence has emerged regarding interventions for prevention and treatment of PTSD symptoms in critical illness survivors.[13,14]

Given this background, our objectives were to evaluate the prevalence of PTSD symptoms in general critical illness survivors via meta-analysis, and to perform a systematic review of the literature to synthesize the following: 1) patient-specific and ICU-related risk factors for PTSD symptoms; 2)

associations between PTSD and health-related quality of life (HRQOL); and 3) effectiveness of prevention and treatment interventions for PTSD symptoms.

Materials and Methods

Search strategy

We searched 5 electronic databases (PubMed, Embase, CINAHL, Psyc INFO, Cochrane Library) from inception through March 5, 2014 to identify eligible studies (Figure 1). We combined controlled vocabulary (MeSH and Emtree) and keyword terms and phrases to define the concepts of posttraumatic stress disorder, psychometrics, critical care and respiratory distress. These terms were "exploded" when applicable. The search strategy was not limited by language of publication. Detailed search strategies for each database are presented in Appendix – Search Strategy. A manual search of the reference lists from all relevant review articles was performed.

Study selection

For inclusion in the systematic review, articles were required to meet the following criteria: (1) study population consisting of adult critical illness survivors, (2) PTSD assessment conducted using a validated measure, and (3) PTSD assessment conducted ≥1 month post-ICU discharge while patients were in their home environment. Articles were excluded from the review if the study population met any of the following criteria: (1) >50% pediatric patients (<16 years), (2) <50% ICU patients, (3) primary focus on patients with a specific illness/disease or from a specialty ICU (e.g., trauma/burn unit, coronary or neurological ICU, etc.), or (4) case series with <10 patients. Abstracts, dissertations not published in a peer-reviewed journal, and review articles were excluded.

Two reviewers independently and sequentially reviewed titles and abstracts, and then full text articles to select eligible studies. All selected titles and abstracts were included in the review of full text

articles. Any disagreement regarding eligibility of full text articles was resolved by consensus of all authors.

Data abstraction

Two reviewers independently abstracted data from each eligible article, with any differences resolved by consensus among abstractors in consultation with an independent co-author (D.M.N). The following were abstracted from each eligible study: design and population, baseline cohort characteristics, inclusion/exclusion criteria, proportion of patients with pre-existing psychiatric illness, timing of and sample size(s) at each PTSD assessment, PTSD assessment instrument (and scoring method), point prevalence of clinically important PTSD symptoms (i.e. PTSD symptom score above a pre-defined threshold), potential PTSD risk factors, and associations between PTSD symptoms and HRQOL. Authors of eligible studies were contacted for additional information or clarifications, when necessary.

Risk of Bias Assessment

Risk of bias assessment for included studies was conducted using the Cochrane Risk of Bias[15] for randomized controlled trials (RCTs) and the Newcastle Ottawa Scale[16] for observational studies.

Statistical Analysis

The Impact of Event Scale (IES) was the most common instrument used for measuring PTSD symptoms. For studies using the IES, we abstracted the following data (or requested these data from study authors when not reported): 1) point prevalence of clinically important PTSD symptoms as indicated by an IES score ≥20 and ≥35 (most commonly used thresholds) and 2) mean (standard deviation) IES score. Given variability among studies in the timing of PTSD assessments, we report pooled PTSD prevalences across two time frames after critical illness: 1 to 6 months and 7 to 12 months. IES-measured PTSD symptom prevalence and mean IES score were pooled using a binomial and linear

random-effects model, respectively, with a random intercept for study. The I^2 statistic was used to evaluate between-study statistical heterogeneity; when the I^2 was >50%, indicating substantial heterogeneity, a sensitivity analysis was performed in which any study with qualitative evidence of heterogeneity was removed and the meta-analysis repeated. We could not assess publication bias due to the small number of studies. STATA 12.1 (Stata Corporation, College Station, TX) was used to conduct all analyses.

Results

Description of Search and Study Characteristics

The authors identified 4,205 citations and reviewed 2,817 unique titles and abstracts (after de-duplication of identified citations) and 712 full-text articles, with 40 publications on 36 unique cohorts meeting eligibility criteria (Figure 1). The 40 publications included 7 randomized controlled trials (RCTs),[13,17-22] 4 cross-sectional studies,[23-26] and 29 prospective cohort studies (Appendix - Table 1),[14,18,25-54] with at least one PTSD assessment completed for 4260 patients, with most assessments occurring between 3 and 12 months after critical illness (Appendix - Table 2). The studies were conducted predominantly in the United Kingdom[13,20,22,24,27,33,34,39,42-44,47,51,53] and United States.[21,29,30,41,52,54]

Risk of Bias Assessment

Risk of bias assessment of the included RCTs demonstrated that randomized sequence generation and allocation concealment were adequate in most studies (Appendix - Table 3). Double-blinding was feasible in only one RCT. Assessment of observational studies demonstrated that most adequately addressed selection, comparability of groups and outcomes (Appendix - Table 4).

Measures and Prevalence of PTSD

In two studies, PTSD symptoms were assessed using a semi-structured psychiatric interview.[25,50] The remaining publications utilized questionnaires, including most commonly: the IES (16 publications),[17,22-24,32-34,36-39,46,47,49,51,53] the IES-Revised (IES-R) (7 publications),[14,18,19,28,35,40,45] and the Posttraumatic Symptom Scale-10 (PTSS-10) (6 publications).[18,21,25,31,52,54] The assessments were conducted in-person, by telephone and by mail in 15[13,21,22,32-35,41,42,44,45,47,50,51,53,54], 15[13,14,19,26,28-31,33,35,40-43,45,49], and 11 studies,[17,19,20,23,24,27,35-39,46,48] respectively (two studies[25,52] did not report how data was collected).

In all studies in this review, the point prevalence of PTSD symptoms ranged from 4 to 62% (Figure 2). The IES (potential score range: 0 to 75) was the most commonly used instrument to assess PTSD symptoms, with higher scores indicating greater intrusion and avoidance symptoms. Via meta-analysis of 6 studies (n=456) that utilized the IES at 1-6 months post-ICU, the pooled mean [95% CI] score was 20 [17-24; I^2=78%], and the pooled prevalence [95% CI] of clinically important PTSD symptoms was 25% [18- 34%; I^2=68%] and 44% [36-52%; I^2=62%] using IES thresholds ≥35 and ≥20, respectively.[22,33,34,36-38,46,51,53] In 698 patients (5 studies), at 7-12 months post-ICU, the pooled mean IES score was 17 [9-24; I^2=97%], and pooled prevalences of PTSD symptoms were 17% [10-26%; I^2=85%] and 34% [22-50%; I^2=93%].[23,34,36-38,46,49,51]

In sensitivity analyses, two studies[33,53] with qualitative evidence of heterogeneity at 1-6 months and one study at 7-12[49] months were removed from the meta-analysis, demonstrating similar results. At 1-6 month follow-up, based on 4 studies (n=385) the pooled mean [95% CI] IES score was 21 [19-22; I^2=0%], and the pooled prevalences [95% CI] of clinically important PTSD symptoms were 24% [20-29%; I^2=0%] and 46% [41-52%; I^2=14%], using IES thresholds ≥35 and ≥20, respectively.[22,33,34,36-38,46,51] At 7-12 months, the pooled mean IES score for 4 studies (n=529) was 19 [16-22] (I^2=75%), and pooled

prevalence of PTSD symptoms was 22% [18-27%] (I^2=36%) and 43% [35-51%] (I^2=63%), respectively.[15,19,21-23,31,37]

Risk Factors for PTSD

Age was not associated with PTSD symptoms in 9 of 15 studies (Appendix - Table 5).[14,24,26,27,29,30,34,35,38,40,43,45-48,50,54] Sex was not associated with PTSD symptoms in 13 of 17 studies.[13,14,26,27,29,32,34,35,38-41,43,45,46,48,49,54] Pre-ICU psychopathology was associated with PTSD symptoms in 5 of 9 studies.[14,25-27,30,42,43,50,53] The 4 studies that did not report an association between pre-ICU psychopathology and PTSD symptoms tended to be smaller (N<60)[14,50,53] or assessed only pre-ICU depression versus all pre-ICU psychopathology.[30]

Sedation in the ICU was evaluated for associations with PTSD symptoms. Greater PTSD symptoms were associated with receipt of benzodiazepines in 2 of 4 studies[14,27,31,40] and higher total dose of benzodiazepines in 1 of 2 studies,[31,54] but not with duration of benzodiazepines in 1 study.[30] Daily interruption of sedation,[21] light versus deep sedation,[19] an analgesia-based sedation protocol,[31] and a no-sedation (only bolus doses of morphine) protocol[18] were not associated with an increase in PTSD symptoms. Duration of delirium or any ICU delirium was not associated with PTSD symptoms in 2 of 2 studies.[30,54]

Corticosteroids administered in the ICU had no association with PTSD symptoms in two studies with sample sizes of <100.[14,29] One of these studies reported greater PTSD symptoms in individuals homozygous for the corticotrophin-releasing hormone binding protein (CRHBP) T/T allele, a gene involved in the hypothalamic-pituitary-adrenal (HPA) axis; corticosteroid exposure differed according to CRHBP genotype.[29]

Severity of illness and ICU length of stay (LOS) were not significantly associated with PTSD symptoms in 11 of 12 studies[14,25,29,34,35,40,43,46-48,50,54] and 12 of 14 studies,[14,24,27,34,35,37,40,43,45-48,50,54] respectively. ICU admission diagnosis was not associated with PTSD symptoms in 7 of 7 studies.[14,27,37,43,45,48,53] nor were mechanical ventilation or mechanical ventilation duration in 5 of 8 studies.[14,30,37,38,40,43,45,50,54]

Early post-ICU memories of frightening ICU experiences (e.g., hallucinations, paranoid delusions, and nightmares were associated with PTSD symptoms in 10 of 12 studies.[13,17,22,31,34,40-42,45,49,51,53,54] Post-ICU psychopathology (e.g., anxiety, depression and substance abuse) was associated with PTSD symptoms in 4 of 4 studies.[40,50,52,53]

Interventions to Reduce PTSD Symptoms

An ICU diary was associated with a significant reduction in PTSD symptoms at 3 to 12 month follow-up in 2 studies (RCT, n=352 and prospective study, n=143),[13,14] and a self-help rehabilitation manual was associated with a significant reduction at 2 months but not at 6 months (RCT, n=126) (Appendix - Table 5).[22] A nurse-led ICU follow-up clinic showed no benefit for PTSD symptoms in 1 RCT (n=286),[20] and a pre-post study of a multidisciplinary follow-up clinic (n=258) found benefit for women, but not men.[32]

Association between PTSD and Health-related Quality of Life (HRQOL)

Six of six studies evaluating the cross-sectional association between PTSD and HRQOL reported greater PTSD symptoms were associated with worse mental health-related quality of life (Appendix -

Table 6).[17,23,26,36,47,54] There was no consistent association between PTSD symptoms and physical function.

Discussion

This systematic review and meta-analysis of PTSD symptoms in critical illness survivors demonstrates clinically important PTSD symptoms occur in 1/5 of patients in the first 12 months post-ICU and are associated with worse HRQOL. Variables associated with PTSD symptoms in ICU survivors include: benzodiazepines in the ICU, early memories of frightening ICU experiences and pre-ICU comorbid psychopathology. Severity of illness, admission diagnosis and ICU LOS are consistently not associated with PTSD symptoms. ICU diaries are associated with a reduction in PTSD symptoms.

The pooled prevalence of clinically important PTSD symptoms (IES score ≥ 35) 1-6 and 7-12 months after ICU discharge was 24% and 22%, respectively. In a sensitivity analysis, two studies in the 1-6 and one study in the 7-12 month intervals were identified for removal from the meta-analysis due to heterogeneity. Unlike the other studies in the meta-analysis, one study[33] removed at 1-6 months assessed PTSD symptoms using multiple instruments at the same time point in the setting of a relatively small sample size, and another study[53] assessed PTSD symptoms relatively early (2 months post-discharge). The study removed at 7-12 months[49] had two important distinctions that might account for its low prevalence estimates: 1) the IES was translated into Spanish and 2) there was a low proportion (15%) of patients with a primary diagnosis of respiratory failure. Statistical measures of heterogeneity improved after the sensitivity analysis with modest changes in the pooled results.

Compared with the 22% pooled prevalence of PTSD symptoms in critical illness survivors, the prevalence of PTSD symptoms following acute coronary syndromes was 12% in one recent meta-analysis

including studies utilizing similar PTSD instruments as in this review.[55] In a prospective cohort study of major traumatic injury patients, 23% had an IES score ≥35 at 1 year follow-up.[56] Although different instruments with possibly stricter thresholds were used, the prevalence of clinically important PTSD symptoms in critical illness survivors in this meta-analysis was generally comparable to survivors war-time combat[57,58] (11-31%), and the World Trade Center attacks[59,60] (11-23%).

Establishing standardized assessments to measure PTSD symptoms in critical illness survivors is important, as highlighted by a comparison between the pooled prevalence of PTSD symptoms at 1 year post-ICU from this meta-analysis and the 7% estimate provided in a recent large (N~400) prospective study published after the systematic review.[61] Notably, the instrument used in the prospective cohort, the PTSD Checklist, was used by only two studies in the systematic review that also reported a lower prevalence of PTSD symptoms than the pooled prevalence from the meta-analysis.[19,29,30] Only two instruments have been validated against clinician diagnostic semi-structured interviews in survivors of critical illness: the PTSS-10 (sensitivity 77% and specificity 97%)[62] and IES-R (area under the receiving operating characteristics curve (AUC) 95% [88 – 100%]).[63,64] A study in this review validated the PTSS-14 against the Posttraumatic Stress Diagnostic Scale (AUC 82-95%).[33] The 36 unique cohorts in this systematic review used eight different questionnaires with substantial variability in scoring, follow-up periods, and risk factors assessed, making comparisons across studies difficult. The field could be advanced by use of common survey instruments validated against “gold standard” diagnostic instruments, with standardized follow-up time point(s), scoring methods and thresholds, and reporting of both continuous and binary (i.e. above threshold) PTSD symptom data.[1,2,65]

Pre-existing psychopathology was the only pre-ICU factor consistently associated with PTSD symptoms. Importantly, and also in line with prior reviews, the following ICU-related factors were

consistently not associated with PTSD symptoms: severity of illness, admission diagnosis, ICU LOS and mechanical ventilation.

In this systematic review, two ICU-related variables had important associations with PTSD: sedation and early memories of frightening ICU experiences. It is unclear if associations between benzodiazepine sedation and PTSD symptoms reflect a true causal relationship or whether patients with high in-ICU anxiety (a possible independent risk factor for PTSD symptoms) simply receive higher doses of sedatives. Sedation may contribute to PTSD symptoms through delirium; however, of the two studies in this systematic review that evaluated the association between in-ICU delirium and later PTSD symptoms, neither found a significant association.[30,54] Similarly, a longitudinal study of PTSD symptoms in ARDS survivors, excluded because it focused on a sub-population of ICU survivors, did not demonstrate a relationship between duration of delirium and later PTSD symptoms.[66] The authors hypothesized that the study lacked statistical power to detect a difference in PTSD symptoms with presence/absence of delirium because virtually all of the patients experienced in-ICU delirium.[66] Perhaps sedation contributes to PTSD symptoms not through the duration of delirium but through an increased recall of in-ICU nightmares/psychotic experiences that may have been enhanced by delirium.[7,42]

There are already several known benefits of interruption of sedation paired with spontaneous breathing trials.[67-70] In this systematic review, interruption of sedation, light versus deep sedation, and analgesia-based sedation did not increase, and in fact, showed trends towards decreased PTSD symptoms. In a longitudinal study of ARDS survivors, high dose opiates were associated greater PTSD symptoms while the duration of exposure to opiates was associated with less PTSD symptoms, suggesting that sufficient pain control may be protective while excessive opiate dosing may contribute to sedation and subsequent PTSD symptoms.[66]

Several reports involving PTSD symptoms in patients surviving specific illness (e.g. cardiac surgery, sepsis, ARDS) as well as wartime combat have demonstrated that corticosteroids may protect against PTSD symptoms, perhaps by their role in consolidation of traumatic memories.[66,71-74] While two studies[29,75] in this review did not find a significant association between corticosteroids in the ICU and PTSD symptoms, one of these studies highlighted that individuals who were homozygous for the CRHBP T/T allele, a gene involved in the HPA axis, had greater PTSD symptoms.[29] Another study, not included in this review because it focused exclusively on cardiac surgery patients, found individuals homozygous for the BCl1 G allele, also involved in the HPA axis, had greater PTSD symptoms.[76]

Since the publication of prior systematic reviews,[6,7,9] there has been increasing focus on interventions to reduce clinically important PTSD symptoms. Two studies in this systematic review reported patients receiving an ICU diary had fewer PTSD symptoms; this intervention has become standard care in some European ICUs (International ICU Diary Network www.icu-diary.org). Another study taking place in a trauma ICU, and therefore not included in this systematic review of general critical illness survivors, found an "early intra-ICU psychological intervention" was associated with less PTSD symptoms.[77] A third promising intervention, a post-ICU discharge telephone-based coping skills intervention, has also shown benefits in reducing PTSD symptoms in a very small (n=7) pilot study.[78] Prolonged exposure therapy, the mainstay of treatment for PTSD in other populations,[79,80] has not been assessed in this population, and its feasibility and benefit remains uncertain.

This systematic review has several important limitations. First, with the exception of one study, PTSD symptoms were assessed using questionnaires. Ideally, studies would utilize a clinician diagnostic semi-structured interview, but this is not feasible in large multi-center studies. The heterogeneity of

sample populations and PTSD symptom instruments makes direct comparison difficult. However, the use of meta-analysis to pool the results of the 11 studies using the IES for PTSD symptom assessment strengthens the assertion that PTSD symptoms are highly prevalent among general critical illness survivors. Additionally, our exclusion of studies focusing on patient populations with a specific illness may affect generalizability of our results. However, some specific ICU survivor populations (e.g., trauma or cardiac surgery patients) may, in fact, be distinct from other survivors in terms of their prevalence of PTSD symptoms and possible risk factors. Finally, although care was taken to identify all potentially relevant studies for this systematic review, it is possible that some studies were inadvertently omitted.

In conclusion, PTSD symptoms occurred in 1/5 of critical illness survivors over 1-year follow-up, with higher prevalences in those who had comorbid psychopathology, received benzodiazepines, and had early post-ICU memories of frightening ICU experiences. Given the association between PTSD symptoms and worse HRQOL, identification of risk factors is important to target patients for prevention/treatment interventions and motivate changes in ICU practices that are associated with subsequent PTSD symptoms. One such intervention, ICU diaries, reduced PTSD symptoms in European studies, but the generalizability of these results deserves further study.

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Chapter 3 – Section A Figures

Figure 1. Flow Diagram

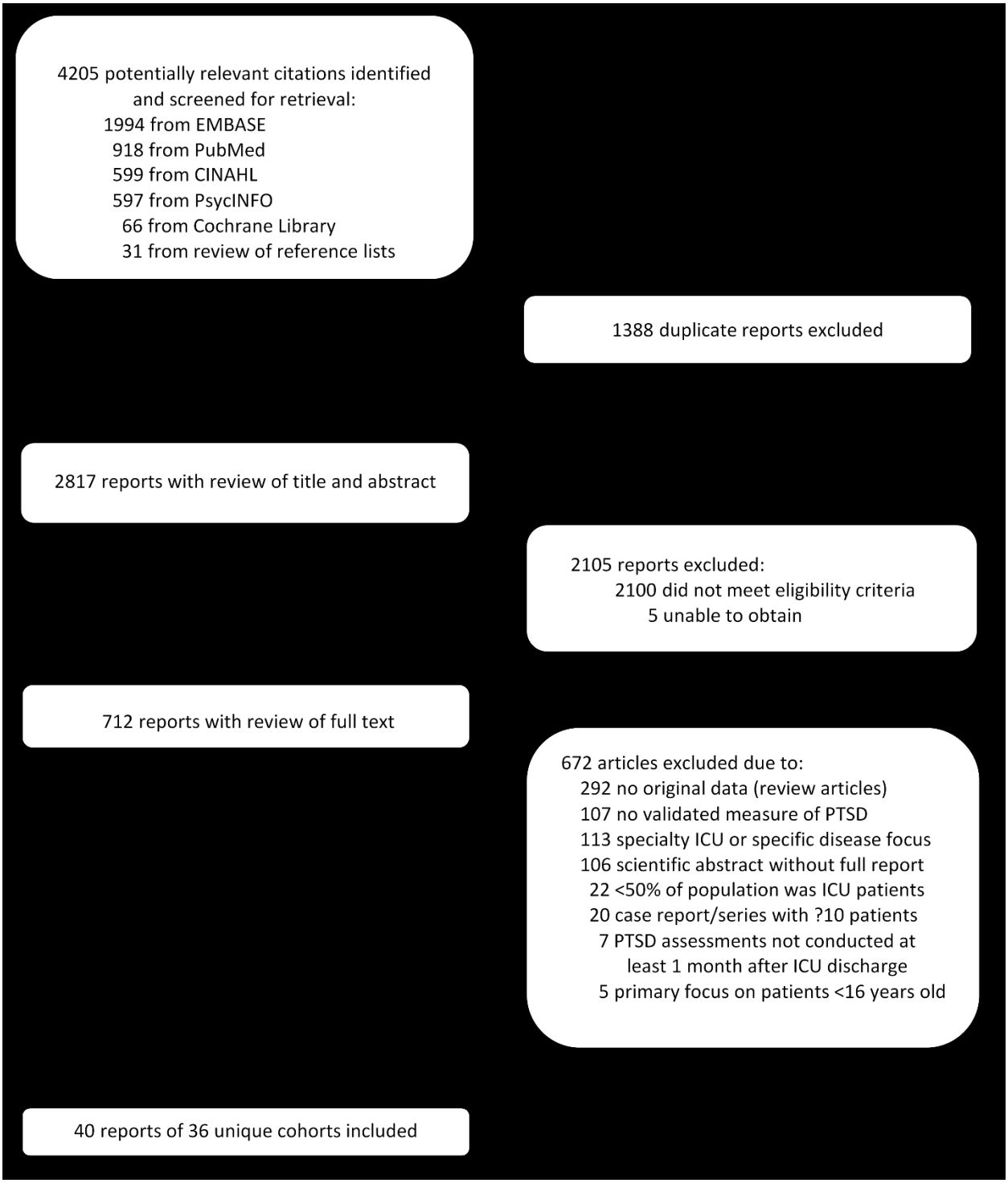
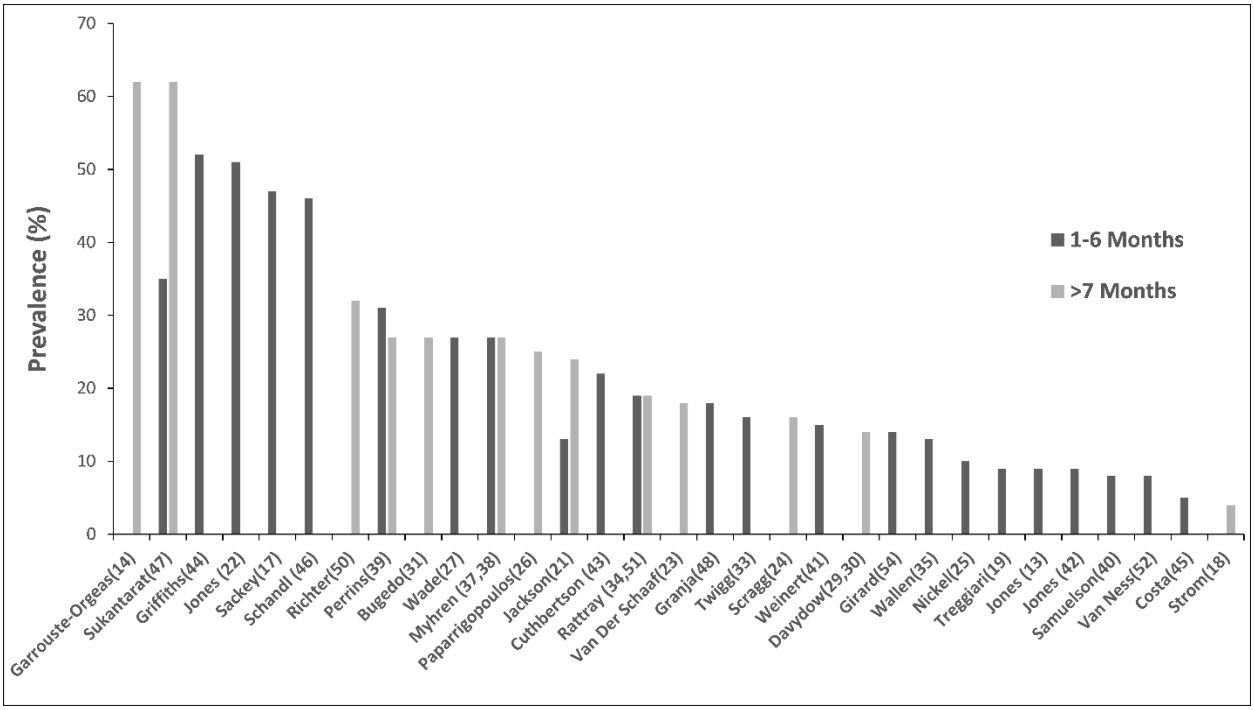


Figure 2. PTSD symptom prevalence in critical illness survivors by study and follow-up time period.



CHAPTER 3:

SECTION B:

Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors:

A One-Year National Multi-Center Study

Minxuan Huang, ScM[1,2]; Ann M. Parker, MD[1,2]; O. Joseph Bienvenu, MD, PhD[1,3]; Victor D. Dinglas, MPH[1,2]; Elizabeth Colantuoni, PhD[1,4]; Ramona O. Hopkins, PhD[5,6,7]; Dale M. Needham, FCPA, MD, PhD[1,2,8] with the NIH NHLBI ARDS Network

[1]Outcomes After Critical Illness and Surgery (OACIS) Group, Johns Hopkins University School of Medicine, Baltimore, MD.
[2]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.
[3]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD.
[4]Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.
[5]Pulmonary and Critical Care Division, Intermountain Medical Center Department of Medicine, Murray, UT.
[6]Center for Humanizing Critical Care, Intermountain Healthcare, Murray, UT
[7]Psychology Department and Neuroscience Center, Brigham Young University, Provo, UT.
[8]Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD.

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ABSTRACT

Objective: To evaluate prevalence, severity, and co-occurrence of, and risk factors for depression, anxiety, and post-traumatic stress disorder (PTSD) symptoms over the first year after ARDS.

Design: Prospective longitudinal cohort study.

Settings: 41 ARDS Network hospitals across the U.S.

Patients: 698 ARDS survivors.

Interventions: None.

Measurements and Main Results: Psychiatric symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale–Revised (IES-R) at 6 and 12 months. Adjusted prevalence ratios for substantial symptoms (binary outcome) and severity scores were calculated using Poisson and linear regression, respectively. During 12 months, a total of 416 of 629 patients (66%) with at least one psychiatric outcome measure had substantial symptoms in at least one domain. There was a high and almost identical prevalence of substantial symptoms (36%, 42%, and 24% for depression, anxiety and PTSD) at 6 and 12 months. The most common pattern of co-occurrence was having symptoms of all 3 psychiatric domains *simultaneously*. Younger age, female sex, unemployment, alcohol misuse, and greater opioids use in the ICU were significantly associated with psychiatric symptoms, while greater severity of illness and ICU length of stay were not associated.

Conclusions: Psychiatric symptoms occurred in two-thirds of ARDS survivors with frequent co-occurrence. Sociodemographic characteristics and in-ICU opioids administration, rather than traditional measures of critical illness severity, should be considered in identifying patients at highest risk for psychiatric symptoms during recovery. Given high co-occurrence, ARDS survivors should be simultaneously evaluated for a full spectrum of psychiatric sequelae to maximize recovery.

INTRODUCTION

Survivors of acute respiratory distress syndrome (ARDS) frequently experience substantial long-term psychiatric symptoms after hospital discharge.(1-10) Pro-inflammatory cytokines, frightening memories experienced in the intensive care unit (ICU), and stressful life changes after hospital discharge may be potential causes for psychiatric symptoms.(6) In ARDS survivors, systematic reviews have reported point prevalences of 17% to 43% for depression, 23% to 48% for anxiety, and 8% to 35% for post-traumatic stress disorder (PTSD) symptoms,(6;7;9) with common risk factors including younger age, female sex, obesity, pre-existing psychiatric illness, lower educational attainment, baseline unemployment, and lower blood glucose in the ICU.(1;3;4;7;9)

However, most existing publications are single-center studies with modest sample sizes that evaluate a single psychiatric domain in isolation. Few studies have evaluated multiple psychiatric outcomes in multiple institutions with large sample sizes.(6;11) These limitations contribute, in part, to conflicting results in evaluating risk factors for psychiatric symptoms after ARDS. To better inform clinicians' and researchers' efforts to effectively identify and treat these important morbidities, additional research is required regarding the prevalence, severity, co-occurrence and risk factors for psychiatric symptoms, using larger-sized, multi-centered, longitudinal studies to simultaneously evaluate commonly reported symptoms.

Hence, our study longitudinally evaluates, over the first year after ARDS, the prevalence, severity and co-occurrence of depression, anxiety, and PTSD symptoms, as well as patient- and critical illness-related risk factors for these symptoms.

METHODS

Study Population

Participants were part of the ARDS Network (ARDSNet) Long-term Outcome Study (ALTOS), a national, multi-center, prospective cohort study evaluating outcomes at 6 and 12 months after enrollment into three recent ARDSNet clinical trials evaluating ICU-based therapies for ARDS patients. The eligibility criteria for these three ARDSNet trials have been published previously and are summarized herein.(12;13) Patients were eligible for recruitment within 48 hours of ARDS onset and within 72 hours of initiation of mechanical ventilation. Major exclusion criteria included severe comorbid malnutrition; lung, liver or neuromuscular diseases; or limitations in life support at time of eligibility.(12;13) For follow-up evaluations in ALTOS, we further excluded survivors from the ARDSNet trials if they had potential cognitive impairment prior to admission (ascertained via medical records and/or patient/proxy report), or were non-English speaking, homeless, or younger than 18 years old. Across all participating sites, patients were managed with simplified versions of lung protective mechanical ventilation and fluid conservative hemodynamic management protocols, with blood glucose control aimed at 80-150 mg/dL (tighter glucose control was permitted). Informed consent was obtained from the patient or a proxy. This study was approved by the Institutional Review Board at Johns Hopkins University and all participating hospitals.

Measurement of Patient- and Critical Illness-Related Exposures

Both patient- and critical illness-related exposures were obtained from ALTOS and the ARDSNet trials. Patient-related baseline exposures included demographics, employment status (unemployed vs. employed), body mass index (BMI), medical comorbidities (diabetes mellitus, prior stroke, and use of hemodialysis), and alcohol misuse. Alcohol misuse was defined by zones 3 and 4 from the Alcohol Use Disorders Identification Test (AUDIT) risk levels, which indicate alcohol consumption in excess of recommended limits. (14) Critical illness-related baseline exposures included admission to a medical (versus surgical) ICU, severity of illness (i.e., Acute Physiology and Chronic Health Evaluation (APACHE) III score, and partial pressure of oxygen in arterial blood to fraction of inspired oxygen (PaO2/FiO2) ratio),

and ARDS risk factor (sepsis versus all others). While in the ICU, the following were collected daily for up to 12 days after enrollment: (1) the Brussels organ failure status for the cardiovascular, pulmonary, coagulation, renal and hepatic systems(15) (modeled as the mean number of organ failures during data collection), (2) use of hemodialysis and vasopressors (modeled as binary variables), (3) use of opioids, corticosteroids, and neuromuscular blockers (modeled as the percentage of ICU days with use), and (4) morning and daily minimum blood glucose (modeled as mean values). Mechanical ventilation duration and ICU length of stay data were also collected.

Measurement of Psychiatric Symptoms

The outcome variables of interest were symptoms of depression, anxiety, and PTSD at 6 and 12 months after ARDS. Anxiety and depression symptoms were measured using the respective subscales of the Hospital Anxiety and Depression Scale (HADS) instrument.(16) Each HADS subscale ranges from 0 to 21, with a higher score indicating worse symptoms and a score $\geq$8 indicating substantial symptoms.(16) PTSD symptoms were measured using the Impact of Event Scale-Revised (IES-R). The IES-R score ranges from 0 to 4, with a higher score indicating worse PTSD symptoms(17) and a score $\geq$1.6 indicating substantial PTSD symptoms in ARDS survivors.(18) Both scales were administered to patients only (i.e. no proxy respondents) by trained research staff via phone for 98% of assessments, otherwise via mail or in-person administration. These scales have evidence of good reliability and validity, and have been frequently used in prior studies evaluating survivors of critical illness.(1;9;18;19)

Statistical Analysis

We compared all exposure variables (see Table 1) by binary categorization of the three psychiatric domains at 6 months using Fisher's exact tests and t-tests. For both the 6- and 12-month time points, correlations of continuous psychiatric symptom scores were calculated using the Spearman correlation coefficient, and co-occurrence of substantial psychiatric symptoms was evaluated by calculating the

proportion of patients who had substantial symptoms in more than one domain. The prevalence and co-occurrence were illustrated via a proportioned Venn diagram utilizing the "pvenn" command (Stata version 13.0, StataCorp, College Station, TX).

Associations between each exposure variable and substantial symptoms for each of the three psychiatric domains (binary outcome variables, as previously defined) were evaluated using Poisson regression. We evaluated these associations separately at 6- and 12-month follow-up; however, due to statistically similar associations at both time points, we adopted a simplified approach combining 6- and 12-month follow-up visits. For this combined approach, the models included an indicator for time (12- vs. 6-month) and were fitted using generalized estimating equations (GEE), with an exchangeable correlation structure and robust variance estimate to account for within-patient clustering over 6- and 12-month follow-ups. For continuous measures of symptom severity for each of the three psychiatric domains, a similar statistical approach was employed using linear regression models. Multivariable regression models were constructed in the same manner as the bivariable models and included all exposure variables that had a potentially significant bivariable association of $p<0.20$ with each psychiatric domain. Regardless of bivariable association, ICU length of stay was included in the multivariable models to standardize evaluation of daily ICU exposure variables, and baseline use of hemodialysis was included to adjust for pre-existing renal disease when including hemodialysis in the ICU in the multivariable models. To evaluate the effect of potential confounding by pre-existing psychiatric comorbidity on the results, we conducted sensitivity analysis using a subgroup of patients (n=203) from 5 of the 12 study sites on whom we prospectively collected baseline psychiatric comorbidity based on medical records. In this analysis, we evaluated the exposure-outcome assessments with vs. without this comorbidity in the original multivariable model.

Standard regression diagnostics were conducted for all models. The linearity assumption was verified by assessing locally weighted scatterplot smoothing of each exposure variable against residuals from the

regression model. Only age demonstrated a non-linear relationship with outcomes, so we categorized age into four quartiles (18-39, 40-49, 50-59, and 60-89 years), with the last quartile (60-89) as the reference. We confirmed that there was no multi-collinearity by evaluating variance inflation factors.(20) Since missing data were rare (<5% of all survivors at each of 6 and 12 months), regression analysis was done using the available data without imputation. P-values were two-sided, and statistical significance was defined as $p<0.05$. All statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX).

RESULTS

Among 1,176 patients enrolled in the three ARDSNet trials, 247 (21%) died by hospital discharge, an additional 44 (5% of hospital survivors) died before re-consent, and 187 (20% of hospital survivors) met ALTOS exclusion criteria, leaving a total of 698 (59%) who survived hospital stay and were eligible and consented for follow-up (Figure 1). A total of 645 (98%) of 656 and 606 (95%) of 635 survivors had follow-up visits at 6 and 12 months, respectively. Among them, 613 (95%) and 576 (95%) completed at least one psychiatric instrument at 6- and 12-month follow-up, respectively, with 629 patients completing at least one psychiatric instrument over one-year longitudinal follow-up.

Participating patients had a mean age of 49 years, with 52% female, 82% white and 49% unemployed prior to hospital admission (Table 1). Patients with substantial psychiatric symptoms during follow-up were more likely ($p<0.05$ based on Fisher's exact and t-tests) to be younger, female, unemployed prior to ARDS, have alcohol misuse history, be less acutely ill (i.e. lower APACHE III score at ICU admission), and receive opioids for a greater proportion of ICU stay (Table 1).

Individual Psychiatric Domains and their Co-occurrence

Among 629 patients with at least one psychiatric measure, 416 (66%) had substantial symptoms in $\geq$1 domain during one-year follow-up. At 6 months (Table 1), the prevalence of substantial symptoms of

depression, anxiety, and PTSD was 36% (222/613), 42% (260/613), and 24% (148/605), respectively, with almost identical prevalence at 12 months (36% (204/574), 42% (241/575), and 23% (132/573)). Across all three domains, the multivariable models demonstrated no significant change in prevalence or severity of psychiatric morbidity over time (Tables 2 and 3). Of patients who had substantial symptoms of depression, anxiety, and PTSD at 6 months, 57%-66% still had the same symptoms at 12 months, and <15% of patients without substantial symptoms at 6 months developed symptoms later.

Continuous scores for psychiatric symptoms during follow-up were correlated as follows: depression and anxiety (Spearman's rho: 0.70-0.72, $p<0.001$), anxiety and PTSD (0.69 at both time points, $p<0.001$), and depression and PTSD (0.58-0.59, $p<0.001$). The majority of survivors (63%) with any psychiatric morbidity (i.e. depression, anxiety, and/or PTSD symptoms) had substantial symptoms in two or more domains. At 6 months, 325 (53%) of 613 patients had substantial symptoms in at least 1 of the 3 domains assessed in this study. Among these symptomatic patients, the most common pattern of co-occurrence of symptoms involved simultaneously having substantial symptoms of depression, anxiety, and PTSD (n=106, 33%), followed by substantial depression and anxiety symptoms (18%), substantial anxiety and PTSD symptoms (7%), and substantial depression and PTSD symptoms (3%) (Figure 2). Similar results were observed at 12 months.

Risk Factors for Substantial Psychiatric Symptoms and Severity

The bivariable and multivariable prevalence ratios for each psychiatric domain by risk factors are reported in Table 2. Female sex, unemployment prior to hospital admission, and alcohol misuse were associated with substantial symptoms in all three psychiatric domains. Younger age was significantly associated with substantial anxiety and PTSD symptoms, and a greater proportion of ICU days with opioids administration was significantly associated with substantial anxiety and depression symptoms (Table 2). Risk factor associations were similar when psychiatric symptoms were modeled as continuous

variables (Table 3). Specifically, female sex, unemployment, and a greater in-ICU opioid use were associated with symptoms in all three domains. Younger age, alcohol misuse, and greater in-ICU neuromuscular blocker use were associated with more severe anxiety and PTSD symptoms.

Sensitivity analysis demonstrated that pre-existing psychiatric comorbidity was associated with each psychiatric domain in continuous analyses and only with anxiety in binary analyses. Adding psychiatric comorbidity in both continuous and binary multivariable models demonstrated relatively little change in the overall results with the risk factors for depression remaining significant, unemployment no longer being significant for anxiety, and female sex no longer being significant for PTSD.

In both binary and continuous analyses, greater severity of illness (i.e., APACHE III, PaO2/FiO2 ratio, number of organ failures, hemodialysis, and vasopressors), consistently was not associated with, or was negatively associated with, psychiatric symptoms. Moreover, there was no association between type of ICU, ARDS risk factor (sepsis vs. others), mechanical ventilation duration, and ICU length of stay with psychiatric symptoms in any analysis (Tables 2 and 3).

DISCUSSION

In this national, multicenter, longitudinal follow-up study evaluating psychiatric symptoms in over 600 ARDS survivors, two-thirds of participants had substantial symptoms in at least one psychiatric domain during 12-month follow-up. There was high prevalence, persistence, and co-occurrence of depression, anxiety, and PTSD symptoms. Severity of illness, mechanical ventilation duration and ICU length of stay were not associated with worse psychiatric symptoms. Younger age, female sex, baseline unemployment, alcohol misuse, and greater in-ICU use of opioids were consistently significant markers for post-ICU psychiatric symptoms.

At 6 months, the prevalence of substantial symptoms of depression, anxiety, and PTSD were high at 36%, 42%, and 24%, without improvement at 12 months. These prevalence rates are much higher than those in the general population,(21;22) but comparable with prior smaller, single-centered studies of ICU survivors.(4-7) Moreover, our findings of the persistence, frequent co-occurrence, and moderate to high correlation of psychiatric symptoms are also built upon prior studies of ICU survivors.(2;5;8;23-26)

Notably, anxiety and depression symptoms observed in this study may reflect pre-ARDS psychiatric morbidity; however, when accounting for pre-ICU psychiatric status, critical illness may remain an independent risk factor for new post-ICU psychiatric morbidity.(27;28) Moreover, PTSD symptoms, reported in approximately one-quarter of survivors in this study, likely represent incident psychiatric symptoms post-ARDS, since the IES-R instrument used in this study specifically addresses patients' symptoms in relation to their critical illness and ICU experience.

Our findings add to the growing body of evidence that psychiatric symptoms are a significant and prolonged burden for ICU survivors, and that patient and critical illness factors may be markers for these symptoms. The positive associations of younger age, female sex and unemployment with psychiatric symptoms are recognized in ICU survivors and other patient populations.(1;4;29-35) Notably, however, our sensitivity analysis suggests that the association of unemployment with anxiety and female sex with PTSD may be a marker for patients who have pre-existing psychiatric comorbidity rather than independent risk factors. While existing findings have been inconsistent about alcohol use disorder as a predictor for developing psychiatric conditions, our study suggests that it is strongly associated with psychiatric symptoms and severe outcomes.(36-40)

A longer duration of opioid exposure was the only ICU-related risk factor consistently and positively associated with symptoms in all three psychiatric domains. A prior study of ARDS survivors demonstrated that a high mean daily dose of opioids (≥100mg of morphine equivalents per day) was

positively associated with PTSD symptoms measured by IES-R, but a greater proportion of ICU days with opioid was negatively associated with PTSD symptoms.(9) It has been speculated that adequate pain control using opioids may have a preventive effect on PTSD.(9;41-43) Unfortunately, data on opioid dosing was not available to further evaluate this issue in our study. Future research in survivors of critical illness should investigate, in greater detail, the potentially complex role of in-ICU opioid administration and dosage.

Of note, our study demonstrated that five different measures of severity of illness, along with mechanical ventilation duration and ICU length of stay, had no positive association with psychiatric symptoms. Notably, a higher APACHE III score was associated with lower symptom scores, which might reflect that patients with higher severity of illness who survived their ICU stay had less pre-existing psychiatric illness or had another unmeasured factor that was protective against post-ICU psychiatric symptoms. Despite these findings contradicting positive associations of illness severity with post-ARDS physical impairments and mortality,(11;44-48) our findings agree with prior studies evaluating psychiatric symptoms in both ARDS and other ICU survivors.(30-32;49;50) Hence, it is critical for clinicians to recognize that patients with anticipated better physical outcomes, due to a lower severity of illness and shorter length of stay, should not be overlooked when considering risk for post-ICU psychiatric symptoms.(9;49;50)

The strengths of this study include being a national, longitudinal, prospective study with large sample size, high retention rate ($\geq$95%), and simultaneous evaluation of prevalence, severity, co-occurrence and risk factors for three common psychiatric morbidities. However, the study has potential limitations. First, our study focused on relatively young ARDSNet trial survivors with exclusions for severe comorbid diseases. Hence, the findings may not be generalizable to other populations. However, comparisons of our findings to the existing literature generally revealed consistency of results, which may support

generalizability. Second, this evaluation was restricted to the variables collected as part of the ARDSNet trials, omitting potentially relevant variables, such as baseline neuropsychological and physical functioning status, ICU exposure to sedatives, dose-related data for the opioid and corticosteroid, and daily pain, sedation and delirium assessments. Inclusion of such variables in future large-scale studies is highly recommended. Third, given its observational design, our study cannot demonstrate cause-effect relationships; hence, the results should be recognized as markers of risk for post-ARDS psychiatric symptoms, rather than as direct causal associations. We could be underpowered to identify a true association between severity of illness and psychiatric symptoms, but prior literature supports our findings. Finally, we used self-reported measures of psychiatric symptoms without ascertaining clinical psychiatric diagnoses and could only determine the prevalence, rather than incidence of depression and anxiety symptoms. However, the HADS and IES-R are commonly used and well-validated instruments.(1;9;18;19) Moreover, they have the advantages of providing both a binary result and a continuous measure of symptom severity, and being feasible to administer to a large geographically dispersed national patient cohort.(9) In addition, the IES-R instrument used in this study evaluates PTSD symptoms with respect to patients' critical illness, thus likely evaluating incident symptoms. The IES-R instrument has high discrimination (area under the receiver operating characteristics = 95%) in screening for a clinical diagnosis of PTSD in ARDS survivors.(18)

CONCLUSION

Two-thirds of ARDS survivors had substantial symptoms of depression, anxiety or PTSD during 12-month follow-up. We observed high co-occurrence among these psychiatric domains, particularly co-occurrence of all three morbidities. Younger age, female sex, unemployment prior to hospital admission, alcohol misuse, and greater in-ICU use of opioids were significant markers for these symptoms. However, traditional risk factors for post-ICU physical impairment were not associated with worse

symptoms. These findings have value in identifying patients at greatest risk of psychiatric symptoms during recovery from critical illness, and emphasize the need to simultaneously evaluate for a full spectrum of potential sequelae to maximize patient recovery.

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Investigators and research staff from National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network sites that participated in this follow-up study: University of Washington, Harborview (*L. Hudson, S. Gundel, C. Hough, M. Neff, K. Sims, A. Ungar, T. Watkins); Baystate Medical Center (*J. Steingrub, M. Tidswell, E. Braden, L. DeSouza, C. Kardos, L. Kozikowski, S. Ouellette); Baylor College of Medicine (K. Guntupalli, V. Bandi, C. Pope, C. Ross); Johns Hopkins University (*R. Brower, H. Fessler, D. Hager, P. Mendez-Tellez, D. Needham, K. Oakjones); Johns Hopkins Bayview Medical Center (J. Sevransky, A. Workneh); University of Maryland (C. Shanholtz, D. Herr, H. Howes, G. Netzer, P. Rock, A. Sampaio, J. Titus); Union Memorial Hospital (P. Sloane, T. Beck, D. Highfield, S. King); Washington Hospital Center (B. Lee, N. Bolouri); Cleveland Clinic Foundation (*H.P. Wiedemann, R.W. Ashton, D.A. Culver, T. Frederick, J.A. Guzman, J.J. Komara Jr, A.J. Reddy); University Hospitals of Cleveland (R. Hejal, M. Andrews, D. Haney); MetroHealth Medical Center (A.F. Connors, S. Lasalvia, J.D. Thornton, E.L. Warren); University of Colorado Hospital, Aurora (*M. Moss, E.L. Burnham, L. Gray, J. Maloney, M. Mealer); Denver Health Medical Center (I. Douglas, K. Overdier, K. Thompson, R. Wolken); Rose Medical Center (S. Frankel, J. McKeehan); Swedish Medical Center (M.L. Warner); Saint Anthony's Hospital (T. Bost, C. Higgins, K. Hodgin); Duke University (*N. MacIntyre, L. Brown, C. Cox, M. Gentile, J. Govert, N. Knudsen); University of North Carolina (S. Carson, L. Chang, S. Choudhury, W. Hall, J. Lanier); Vanderbilt University (*A.P. Wheeler, G.R. Bernard, M. Hays, S. Mogan, T.W. Rice); Wake Forest University (*R.D. Hite, A. Harvey, P.E. Morris, Mary Ragusky); Moses Cone Memorial Hospital (P. Wright, S. Groce, J. McLean, A. Overton); University of Virginia (J. Truwit, K. Enfield, M. Marshall); Intermountain Medical Center (*A. Morris, *C. Grissom, A. Austin, S. Barney, S. Brown, J. Ferguson, H. Gallo, T. Graydon, E. Hirshberg, A. Jephson, N. Kumar, M. Lanspa, R. Miller, D. Murphy, J. Orme, A. Stowe, L. Struck, F. Thomas, D. Ward,); LDS Hospital (P. Bailey, W. Beninati, L. Bezdjian, T. Clemmer, S. Rimkus, R. Tanaka, L. Weaver); McKay Dee Hospital (C. Lawton, D. Hanselman); Utah Valley Regional Medical Center (K. Sundar, W. Alward, C. Bishop, D. Eckley, D. Harris, T. Hill, B. Jensen, K. Ludwig, D.

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*Principal investigator.

Chapter 3 – Section B Tables

Table 1. Baseline characteristics for all patients and by psychiatric symptoms at 6 months after acute respiratory distress syndrome

Variable[a]	Total (n=613)	Depression Symptoms, n (%)		Anxiety Symptoms, n (%)		PTSD Symptoms[b], n (%)	
		Positive (HADS ≥8) n=222 (36%)	Negative (HADS <8) n=391 (64%)	Positive (HADS ≥8) n=260 (42%)	Negative (HADS <8) n=353 (58%)	Positive (IES-R ≥1.6) n=148 (24%)	Negative (IES-R <1.6) n=457 (76%)
Baseline patient data							
Age, mean (SD) year	49 (15)	48 (12)	49 (16)	48 (12)	50 (16)	47 (12)	50 (15)
Female, N (%)	316 (52)	127 (57)	189 (48)	155 (60)	161 (46)	100 (68)	213 (47)
White, N (%)	485 (82)	174 (81)	311 (82)	211 (84)	274 (80)	108 (78)	371 (83)
Unemployed, N (%)	296 (49)	130 (59)	166 (43)	143 (56)	153 (44)	88 (60)	205 (45)
BMI, mean (SD) kg/m^2	30 (8)	31 (8)	30 (8)	31 (8)	30 (8)	31 (8)	30 (8)
Diabetes, N (%)	146 (24)	52 (23)	94 (24)	62 (24)	84 (24)	32 (22)	110 (24)
Stroke, N (%)	9 (2)	5 (2)	4 (1)	4 (2)	5 (1)	4 (3)	4 (1)
Hemodialysis, N (%)	14 (2)	9 (4)	5 (1)	7 (3)	7 (2)	6 (4)	8 (2)
Alcohol misuse, N (%)	126 (22)	52 (25)	74 (20)	60 (24)	66 (20)	36 (26)	88 (21)
Baseline intensive care data							
Admission to medical ICU, N (%)	350 (57)	124 (56)	226 (58)	151 (58)	199 (56)	86 (58)	259 (57)
APACHE III, mean (SD)	86 (26)	82 (25)	88 (26)	83 (26)	88 (25)	83 (26)	87 (25)
PaO2/FiO2, mean (SD)	204 (73)	209 (76)	200 (72)	202 (65)	205 (79)	207 (71)	202 (74)
Sepsis as ARDS risk factor, N (%)	467 (76)	157 (71)	310 (79)	195 (75)	272 (77)	108 (73)	352 (77)
Daily intensive care data							
No. of organ failures[c], mean (SD)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)
Any hemodialysis, N (%)	76 (14)	22 (11)	54 (15)	24 (10)	52 (17)	19 (14)	56 (14)
Any vasopressor use, N (%)	325 (53)	110 (50)	215 (55)	137 (53)	188 (53)	81 (55)	240 (53)
% of days with opioids, mean (SD)	73 (30)	78 (28)	70 (31)	76 (28)	70 (32)	79 (27)	71 (31)
% of days with corticosteroids, mean (SD)	21 (35)	23 (37)	20 (34)	21 (36)	20 (34)	24 (37)	20 (34)
% of days with neuromuscular blocker, mean (SD)	5 (13)	5 (14)	5 (13)	6 (14)	4 (13)	6 (15)	5 (13)
Morning glucose, mean (SD) mg/dl,	127 (26)	127 (26)	127 (26)	126 (26)	128 (26)	126 (26)	128 (26)
Minimum glucose, mean (SD) mg/dl	110 (23)	110 (25)	111 (21)	108 (23)	112 (22)	108 (20)	111 (23)
Other intensive care data							

Ventilation duration, mean (SD) day	11 (10)	11 (10)	11 (10)	10 (8)	11 (11)	11 (9)	11 (10)
ICU length of stay, mean (SD) day [d]	14 (11)	14 (11)	14 (11)	13 (10)	15 (12)	14 (10)	14 (11)

Abbreviations: ARDS (acute respiratory distress syndrome), PTSD (post-traumatic stress disorder), HADS (Hospital Anxiety and Depression Scale), IES-R (Impact of Event Scale – Revised), SD (standard deviation), BMI (body mass index), ICU (intensive care unit), APACHE III (Acute Physiology and Chronic Health Evaluation III), PaO2/FiO2 (ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen).

[a] Percentages may not add up to 100% due to rounding. Missing data for each variable (N): white (19), unemployed (10), BMI (2), alcohol misuse (42), APACHE III score (17), PaO2/FiO2 ratio (19), any hemodialysis (58), % of days with opioids (130), % of days with corticosteroids (120), % of days with neuromuscular blocker (130), morning glucose (1), and minimum glucose (101).

[b] Missing PTSD assessments for 8 (1%) of 613 patients.

[c] Data represent the average number of organ failures during ICU stay, using the Brussels scoring system(20) for the following five organ systems (with definition of organ failure): cardiac (systolic blood pressure $\leq$90 mmHg or use of vasopressor), pulmonary (PaO2/FiO2 ratio $\leq$300), coagulation (platelets $\leq$80 x 10^9/L), renal (creatinine $\geq$2.0 mg/dL) and hepatic (bilirubin $\geq$2.0 mg/dL).

[d] Median and inter-quartile range (IQR) of ICU length of stay was 10 (7-16) days.

Table 2. Variables associated with presence versus absence of substantial psychiatric symptoms

	Prevalence ratio (95% CI) of substantial psychiatric symptoms[a,b,c]					
	Depression		Anxiety		PTSD	
Variables	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**
Baseline patient data						
Age quartile (younger vs. older)[d]	1.03 (0.95, 1.12)		1.13 (1.05, 1.21)	**1.16 (1.07, 1.26)**	1.22 (1.10, 1.36)	**1.23 (1.08, 1.41)**
Female	1.24 (1.02, 1.50)	**1.26 (1.01, 1.58)**	1.41 (1.19, 1.66)	**1.43 (1.18, 1.74)**	1.78 (1.37, 2.32)	**1.80 (1.31, 2.48)**
White	0.99 (0.78, 1.26)		1.12 (0.89, 1.40)		0.83 (0.62, 1.13)	
Unemployed	1.50 (1.24, 1.83)	**1.35 (1.09, 1.69)**	1.31 (1.11, 1.55)	**1.26 (1.05, 1.52)**	1.51 (1.17, 1.95)	**1.40 (1.03, 1.90)**
BMI, per 10 kg/m^2	1.07 (0.96, 1.20)		1.11 (1.01, 1.22)	**1.14 (1.03, 1.26)**	1.07 (0.93, 1.24)	
Diabetes	1.06 (0.86, 1.30)		0.99 (0.82, 1.20)		0.85 (0.63, 1.14)	
Stroke	1.39 (0.74, 2.58)		1.04 (0.49, 2.18)		1.61 (0.76, 3.43)	
Hemodialysis	1.29 (0.82, 2.03)	1.54 (0.86, 2.75)	1.05 (0.63, 1.77)	1.26 (0.75, 2.12)	1.39 (0.72, 2.67)	
Alcohol misuse	1.22 (0.99, 1.50)	**1.39 (1.09, 1.77)**	1.19 (0.99, 1.44)	**1.45 (1.18, 1.79)**	1.35 (1.02, 1.79)	**1.79 (1.31, 2.46)**
Baseline intensive care data						
Admission to medical ICU	0.99 (0.82, 1.20)		1.02 (0.87, 1.21)		1.00 (0.77, 1.28)	
APACHE III, per 20 unit	0.90 (0.83, 0.97)	**0.90 (0.82, 0.99)**	0.89 (0.84, 0.96)	0.95 (0.88, 1.02)	0.89 (0.80, 0.98)	**0.88 (0.79, 0.98)**
PaO2/FiO2, per 20 unit	1.01 (0.98, 1.04)		0.99 (0.97, 1.01)		1.01 (0.98, 1.04)	
Sepsis as ARDS risk factor	0.88 (0.71, 1.08)		0.99 (0.82, 1.20)		0.91 (0.68, 1.21)	
Daily intensive care data						
No. of organ failures	0.90 (0.78, 1.05)	0.94 (0.76, 1.18)	0.84 (0.73, 0.96)	0.88 (0.73, 1.07)	0.99 (0.81, 1.21)	
Any hemodialysis	0.66 (0.47, 0.92)	0.69 (0.45, 1.04)	0.67 (0.48, 0.91)	0.77 (0.53, 1.12)	0.95 (0.64, 1.43)	
Any vasopressor use	0.94 (0.78, 1.14)		0.98 (0.83, 1.16)		1.12 (0.87, 1.44)	
% of days with opioids, per 20%	1.10 (1.02, 1.19)	**1.11 (1.03, 1.20)**	1.07 (1.01, 1.14)	**1.08 (1.01, 1.15)**	1.13 (1.02, 1.25)	1.09 (0.98, 1.22)
% of days with corticosteroids, per 20%	1.02 (0.96, 1.08)		1.02 (0.97, 1.07)		1.05 (0.98, 1.13)	1.04 (0.96, 1.12)
% of days with neuromuscular blocker, per 20%	1.00 (0.87, 1.17)		1.12 (1.02, 1.24)	1.12 (0.99, 1.27)	1.14 (0.96, 1.35)	**1.23 (1.02, 1.49)**
Morning glucose, per 20 mg/dL	1.01 (0.94, 1.09)		0.98 (0.92, 1.05)		0.96 (0.87, 1.06)	
Minimum glucose, per 20 mg/dL	1.00 (0.91, 1.10)		0.96 (0.87, 1.05)		0.94 (0.84, 1.06)	
Other intensive care data						
Mechanical ventilation duration, per week	1.02 (0.95, 1.08)		0.99 (0.93, 1.05)		1.02 (0.94, 1.11)	

ICU length of stay , per week	1.01 (0.95, 1.07)	1.00 (0.93, 1.08)	0.98 (0.93, 1.03)	0.95 (0.88, 1.02)	1.00 (0.92, 1.08)	0.93 (0.83, 1.04)
Change at 12 vs. 6 month follow-up[e]		1.00 (0.89, 1.13)		0.91 (0.83, 1.01)		0.90 (0.77, 1.06)

Abbreviations: CI (confidence interval), PTSD (post-traumatic stress disorder), BMI (body mass index), ICU (Intensive Care Unit), APACHE III (Acute Physiology and Chronic Health Evaluation III), PaO2/FiO2 (ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen), ARDS (acute respiratory distress syndrome).

[a] Presence of substantial symptoms of depression, anxiety and PTSD was defined by Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores $\geq$8 and an Impact of Event Scale – Revised (IES-R) score $\geq$1.6. Results are presented as prevalence ratios, calculated by Poisson regression models using generalized estimating equations (GEE) with robust variance estimate, an exchangeable correlation structure, and an indicator for time (12- vs. 6-month follow-up).

[b] Variables included in multivariable analyses are those from bivariable analyses that were associated (at $p < 0.20$) with each outcome measure of depression, anxiety, or PTSD symptoms.

[c] All the significant associations ($p<0.05$) in multivariable models are highlighted in bold.

[d] Age quartiles in years: 18-39 (quartile 1), 40-49 (quartile 2), 50-59 (quartile 3), 60-89 (quartile 4). Quartile 4 (60-89) was used as the reference group.

[e] Represents the change in outcome proportions, between 12- vs. 6-month follow-up, after adjusting for the other variables.

Table 3. Variables associated with severity of psychiatric symptoms

	Increase (95% CI) in psychiatric symptom score[a,b,c]					
	HADS-Depression		HADS-Anxiety		IES-R	
Variables	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**
Baseline patient data						
Age quartile (younger vs. older)[d]	0.03 (-0.30, 0.36)		0.67 (0.34, 1.01)	**0.70 (0.30, 1.10)**	0.13 (0.07, 0.19)	**0.14 (0.07, 0.21)**
Female	1.28 (0.57, 1.99)	**0.91 (0.11, 1.71)**	1.63 (0.90, 2.36)	**1.81 (0.94, 2.67)**	0.33 (0.19, 0.46)	**0.38 (0.22, 0.54)**
White	-0.13 (-1.06, 0.81)		0.24 (-0.72, 1.20)		-0.08 (-0.25, 0.09)	
Unemployed	2.04 (1.34, 2.75)	**1.74 (0.95, 2.54)**	1.30 (0.56, 2.04)	**1.22 (0.36, 2.09)**	0.21 (0.08, 0.35)	**0.20 (0.05, 0.36)**
BMI, per 10 kg/m^2	0.47 (0.03, 0.91)	0.15 (-0.35, 0.65)	0.33 (-0.12, 0.79)	0.39 (-0.16, 0.95)	0.06 (-0.02, 0.14)	0.10 (-0.01, 0.20)
Diabetes	0.16 (-0.68, 1.00)		-0.39 (-1.26, 0.48)		-0.13 (-0.29, 0.02)	-0.02 (-0.21, 0.17)
Stroke	0.95 (-2.08, 3.99)		0.47 (-2.66, 3.61)		0.14 (-0.45, 0.73)	
Hemodialysis	0.42 (-2.01, 2.85)	0.82 (-1.91, 3.55)	-0.92 (-3.42, 1.59)	0.03 (-3.06, 3.12)	0.19 (-0.26, 0.64)	
Alcohol misuse	0.55 (-0.34, 1.43)		0.88 (-0.04, 1.80)	**1.88 (0.81, 2.95)**	0.20 (0.03, 0.36)	**0.40 (0.21, 0.60)**
Baseline intensive care data						
Admission to medical ICU	0.13 (-0.60, 0.85)		-0.01 (-0.75, 0.74)		-0.04 (-0.17, 0.10)	
APACHE III, per 20 unit	-0.39 (-0.67, -0.12)	**-0.36 (-0.68, -0.03)**	-0.52 (-0.81, -0.23)	**-0.44 (-0.79, -0.08)**	-0.06 (-0.11, -0.01)	**-0.07 (-0.13, -0.01)**
PaO2/FiO2, per 20 unit	0.05 (-0.05, 0.15)		-0.01 (-0.12, 0.09)		0.00 (-0.02, 0.02)	
Sepsis as ARDS risk factor	-0.41 (-1.25, 0.43)		-0.22 (-1.09, 0.65)		-0.12 (-0.27, 0.04)	-0.03 (-0.23, 0.17)
Daily intensive care data						
No. of organ failures	-0.61 (-1.18, -0.04)	-0.51 (-1.30, 0.28)	-0.69 (-1.28, -0.11)	-0.28 (-1.13, 0.57)	-0.04 (-0.15, 0.07)	
Any hemodialysis	-1.45 (-2.55, -0.35)	-0.64 (-2.01, 0.74)	-1.31 (-2.43, -0.18)	-0.69 (-2.16, 0.78)	-0.03 (-0.24, 0.17)	
Any vasopressor use	-0.06 (-0.78, 0.65)		0.30 (-0.44, 1.04)		0.07 (-0.06, 0.21)	
% of days with opioids, per 20%	0.41 (0.14, 0.67)	**0.42 (0.16, 0.69)**	0.39 (0.12, 0.67)	**0.39 (0.10, 0.68)**	0.09 (0.04, 0.13)	**0.07 (0.02, 0.12)**
% of days with corticosteroids, per 20%	0.09 (-0.14, 0.32)		0.08 (-0.16, 0.32)		0.03 (-0.01, 0.08)	0.02 (-0.02, 0.06)
% of days with neuromuscular blocker, per 20%	0.10 (-0.50, 0.70)		0.68 (0.07, 1.30)	**0.67 (0.03, 1.31)**	0.12 (0.01, 0.23)	**0.14 (0.02, 0.25)**

Morning glucose, per 20 mg/dL	0.01 (-0.27, 0.28)		-0.17 (-0.46, 0.11)		-0.01 (-0.07, 0.04)	
Minimum glucose, per 20 mg/dL	-0.13 (-0.48, 0.22)		-0.31 (-0.67, 0.06)	-0.32 (-0.73, 0.10)	-0.03 (-0.09, 0.04)	
Other intensive care data						
Mechanical ventilation duration, per week	0.07 (-0.19, 0.33)		-0.07 (-0.34, 0.19)		0.02 (-0.03, 0.07)	
ICU length of stay, per week	0.03 (-0.20, 0.26)	0.01 (-0.26, 0.27)	-0.09 (-0.33, 0.14)	-0.25 (-0.54, 0.05)	0.01 (-0.03, 0.06)	-0.04 (-0.09, 0.01)
Change at 12 vs. 6 month follow-up [e]		-0.01 (-0.35, 0.33)		-0.30 (-0.70, 0.09)		-0.06 (-0.14, 0.01)

Abbreviations: CI (confidence interval), HADS (Hospital Anxiety and Depression Scale), IES-R (Impact of Event Scale – Revised), BMI (body mass index), ICU (Intensive Care Unit), APACHE III (Acute Physiology and Chronic Health Evaluation III), PaO2/FiO2 (ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen), ARDS (acute respiratory distress syndrome).

[a] Results are presented as the mean difference in HADS-depression, HADS-anxiety, and IES-R scores, calculated by linear regression models using generalized estimating equations (GEE), an exchangeable correlation structure, and an indicator for time (12- vs 6-month follow-up).

[b] Variables included in multivariable analyses are those from bivariable analyses that were associated (at $p < 0.20$) with each outcome measure of psychiatric symptom score.

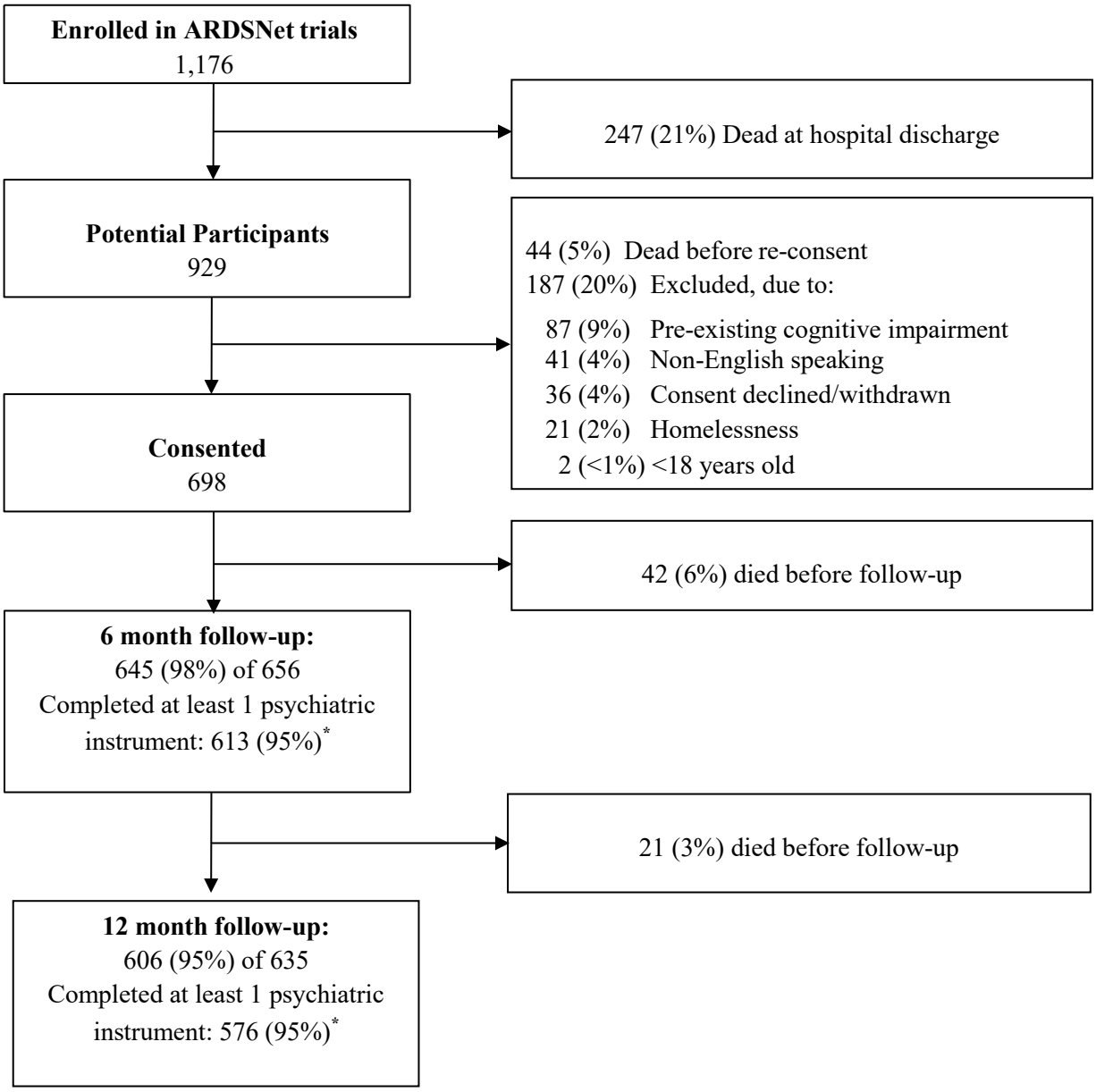
[c] All the significant associations ($p<0.05$) in multivariable models are highlighted in bold.

[d] Age quartiles in years: 18-39 (quartile 1), 40-49 (quartile 2), 50-59 (quartile 3), 60-89 (quartile 4). Quartile 4 (60-89) was used as the reference group.

[e] Represents the difference in mean outcome scores, between 12- vs. 6-month follow-up, after adjusting for the other variables.

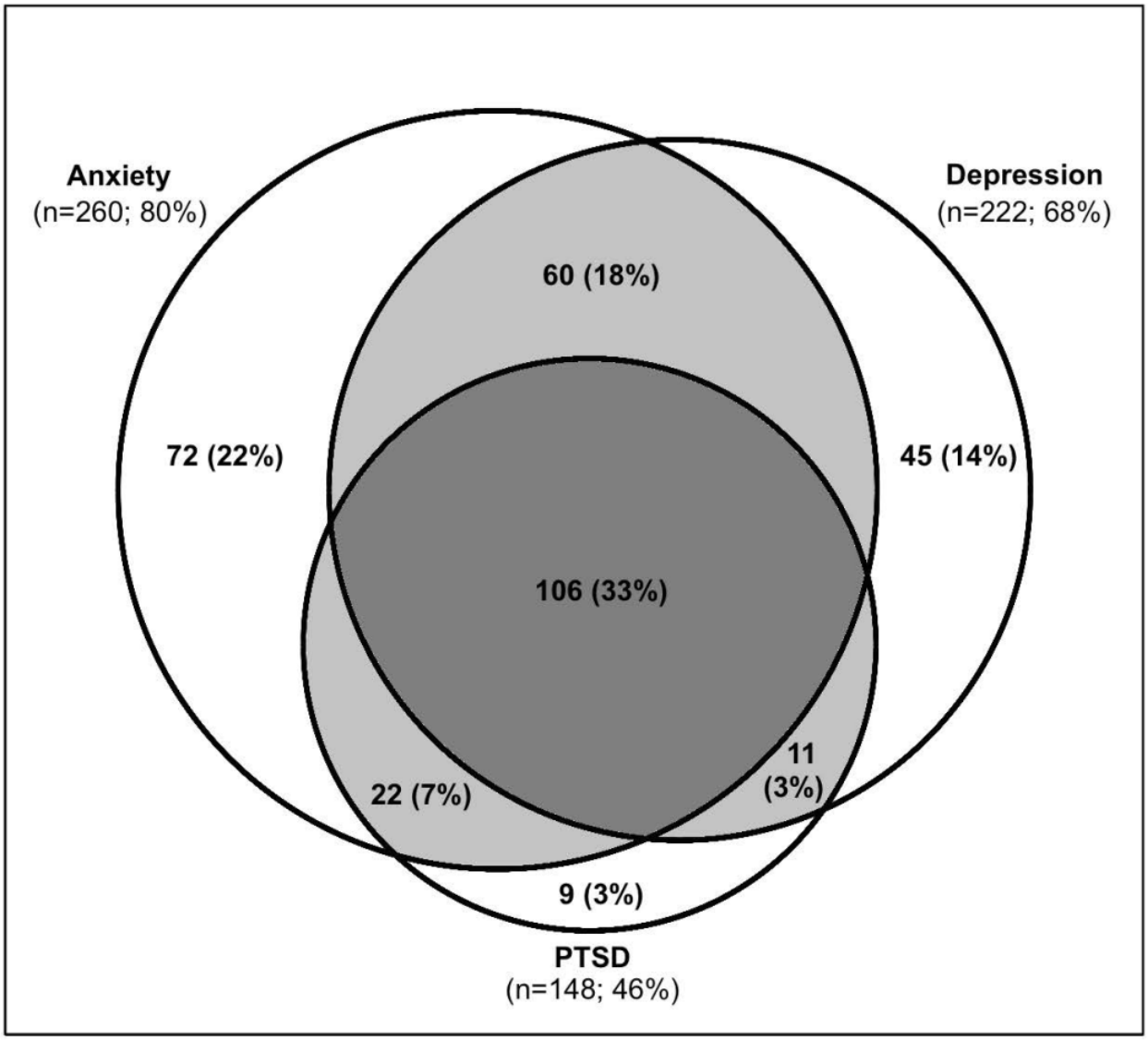
Chapter 3 – Section B Figures

Figure 1. Patient flow diagram.



* Reasons for not completing psychiatric assessments at 6 and 12 months, respectively: declined 8 and 7, physically incapable 7 and 5, cognitively incapable 6 and 4, receiving mechanical ventilation 3 and 3, psychiatric issues 2 and 3, incarcerated 2 and 2, unable to contact 3 and 1, lack of time 0 and 1, and other reason 1 and 4.

Figure 2. Venn diagram of co-occurrence of anxiety, depression, and PTSD symptoms among 325 patients with any psychiatric morbidity at 6-month follow-up. (Light grey area indicates co-occurrence of two psychiatric symptoms; dark grey area indicates co-occurrence of all three psychiatric symptoms).



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CHAPTER 4

SECTION A

A Quality Improvement Project Sustainably Decreases Time to Active Physical Therapy Intervention in Acute Lung Injury Patients

Victor D. Dinglas, MPH[1,2*], Ann M. Parker, MD[1,2*], Dereddi Raja S. Reddy, MD[3], Elizabeth Colantuoni, PhD[2,4], Jennifer M. Zanni, PT, DScPT[2,5], Alison E. Turnbull, DVM, MPH, PhD[1,2], Archana Nelliot, BS[1,2], Nancy Ciesla, DPT, MS[1,2], Dale M. Needham, FCPA, MD, PhD[1,2,5]

[1]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine
[2]Outcomes After Critical Illness and Surgery (OACIS) Group, Johns Hopkins University
[3]Division of Pulmonary and Critical Care Medicine, Mayo Clinic
[4]Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health
[5]Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine
*Co-first authors with equal contribution to the manuscript.
Author contributions: All authors contributed to the study design, acquisition, analysis and/or interpretation of data. VDD and AMP drafted the manuscript. All authors reviewed and provided final approval for the manuscript.

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Abstract

RATIONALE: Rehabilitation started early during an intensive care unit (ICU) stay is associated with improved outcomes and is the basis for many quality improvement (QI) projects showing important changes in practice. However, little evidence exists regarding whether such changes are sustainable in real-world practice.

OBJECTIVE: To evaluate the sustained effect of a QI project on the timing of initiation of active physical therapy intervention in acute lung injury (ALI) patients.

METHODS: This was a pre-post evaluation using prospectively collected data involving consecutive ALI patients admitted pre-QI (October 2004-April 2007, n=120) versus post-QI (July 2009-July 2012, n=123) from a single medical ICU.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was time to first active physical therapy intervention, defined as strengthening, mobility or cycle ergometry exercises. Among ICU survivors, more patients in the post-QI versus pre-QI group received physical therapy in the ICU (89% vs. 24%, p<0.001) and were able to stand, transfer or ambulate during physical therapy in the ICU (64% vs. 7%, p<0.001). Among all patients in the post-QI versus pre-QI group, there was a shorter median [IQR] time to first physical therapy (4 [2,6] vs. 11 days [6,29], p<0.001) and a greater median (IQR) proportion of ICU days with physical therapy after initiation (50% [33%,67%] vs. 18% [4%,47%], p=0.003). In multivariable regression analysis, the post-QI period was associated with shorter time to physical therapy (adjusted hazard ratio [95% confidence interval]: 8.38 [4.98,14.11], p<0.001), with this association significant for each of the 5 years during the post-QI period. The following variables were independently associated with a longer time to physical therapy: higher SOFA score (0.93 [0.89,0.97]), higher FiO2 (0.86 [0.75,0.99] for each 10% increase), use of an opioid infusion (0.47 [0.25,0.89), and deep sedation (0.24 [0.12,0.46]).

CONCLUSIONS: In this single-site, pre-post analysis of ALI patients, an early rehabilitation QI project was independently associated with a substantial decrease in the time to initiation of active physical therapy intervention that was sustained over 5 years. Over the entire pre-post period, severity of illness and sedation were independently associated with a longer time to initiation of active physical therapy intervention in the ICU.

Introduction

As short-term mortality for patients with acute lung injury (ALI) decreases,[1-4] there is a growing population of survivors who frequently experience long-lasting physical impairments.[5-10] Patients with ALI are often exposed to prolonged immobilization, contributing to neuromuscular weakness that has a negative impact on the survivors' physical function and quality of life for years following discharge from the intensive care unit (ICU).[6-11] Early rehabilitation, including physical therapy in the ICU, reduces neuromuscular weakness and improves physical function and quality of life in ALI survivors.[12-20]

Despite evidence showing improved outcomes with early physical therapy in the ICU, many critically ill patients remain immobilized for prolonged periods, with initiation of physical therapy delayed until mechanical ventilation is discontinued and the patient is discharged from the ICU.[14,19,21-25] There are several potentially modifiable barriers to incorporating early physical therapy into routine clinical practice, including: inadequate multidisciplinary education, staffing and collaboration; insufficient knowledge; and deep sedation.[16,21,24,26,27] Multiple centers have addressed such potential barriers to early physical therapy by successfully implementing structured quality improvement (QI) projects.[28-36] These projects, along with clinical trials and observational studies, have demonstrated that early physical therapy in critically ill patients is safe and feasible.[12-16,18,26,27,37-41] However, there is little published evidence assessing whether QI projects can be sustained beyond the period of their initial implementation and evaluation. Sustainability is an important aspect in evaluating QI interventions since, over time, clinician practice may revert to earlier routines when there is a focus on new areas of practice.[42]

Hence, our objective is to evaluate the sustainability of an early rehabilitation QI project in a single medical ICU (MICU) and to evaluate how the QI project and other patient and ICU-related factors are associated with the timing of initiation of active physical therapy intervention in the MICU.

Methods

Study design

An early rehabilitation QI project was conducted from May to August 2007 at the Johns Hopkins Hospital MICU. This project aimed to reduce modifiable barriers to early rehabilitation interventions for all MICU patients.[28,43] Details of this QI project are provided elsewhere[28,43] and summarized herein. The QI project followed a pre-established structured methodology[43,44] and included the following components: 1) changing the default MICU activity order from "bed rest" to "as tolerated"; 2) encouraging a change in sedation practice from continuous infusions to "as needed" boluses; 3) establishing simple guidelines for consultation to physical therapy; 4) establishing safety guidelines for initiating early rehabilitation; and 5) full-time dedicated MICU rehabilitation therapist staffing.[28] The project was planned and implemented via a multidisciplinary team that met weekly to discuss and evaluate the project.

After evaluation of the QI project, the hospital administration funded an ongoing, early rehabilitation program starting the next fiscal year, July 2008 onwards. In addition to maintaining the QI project components described above, a new protocol for sedation management and delirium screening was implemented to formalize changes made during the QI project.[45] Moreover, to further promote sustainability, the multidisciplinary weekly meetings continued with a focus on identifying and addressing new barriers, evaluating individual patient needs, inspiring innovation in early rehabilitation practices,[46-48] and continuing interdisciplinary education and collaboration with >20 physical therapists who worked in the MICU during the post-QI period. Moreover, safety events[37,39] and mobility milestones continued to be evaluated with feedback provided, at least monthly, in the multidisciplinary meetings. Meetings with hospital administrators, highlighting the program's successes and sustained reduction in ICU length of stay[49] were scheduled at least twice per year.

To evaluate the sustainability of a change in the timing of initiation of active physical therapy intervention, we conducted a pre-post comparison study using prospectively collected data. Data for the pre-QI control period was obtained from a prospective cohort study of consecutive ALI patients admitted to the Johns Hopkins MICU from October 2004 to April 2007.[50] To evaluate the sustainability of the QI project, data for the post-QI period started one year after initiation of the early rehabilitation program (i.e. July 2009 onward). These data were obtained from a pre-existing clinical registry of consecutive patients admitted to the Johns Hopkins MICU from July 2009 until July 2012. For both the pre- and post-QI groups, all patients evaluated in this analysis were consecutive mechanically ventilated patients meeting the American-European Consensus Conference criteria for ALI.[51] The prospective cohort study providing the pre-QI control group data excluded patients with any of the following characteristics: (1) pre-existing cognitive impairment, (2) non-English speaking, (3) life expectancy <6 months due to a pre-existing illness, (4) limitations in care (e.g., an order for no vasopressors) at time of meeting ALI criteria, and (5) >5 days of mechanical ventilation prior to ALI or transfer from another ICU with pre-existing ALI (>24 hours). To ensure comparability, these same exclusion criteria were applied to the post-QI group.

Primary Outcome

The primary outcome is the time (in days) from ALI onset to initiation of active physical therapy intervention during the patient's index MICU admission. We defined active physical therapy intervention as providing strengthening, mobility, and/or cycle ergometry exercises, based on physical therapist documentation.

Secondary Outcome

Physiological abnormalities and potential safety events were not collected for the pre-QI period. These events were prospectively collected during the post-QI period and defined as any of the following: (1) removal, dislodgment, disruption, or dysfunction of airway, feeding tube, chest tube, vascular access, cardiac device, or wound dressing; (2) cardiopulmonary changes including arrhythmia, desaturation, and hyper- and hypotension, , (3) falls, (4) cardiac arrest, and (5) death.[37]

Covariates

Patient and ICU-related variables collected from the medical record were included in the analysis. Patient variables were age, sex, race, and body mass index (BMI). Baseline comorbidities were measured using the Charlson[52] and Functional[53] comorbidity indices. ICU-related variables were ICU admission diagnosis category and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score within the first 24 hours of ICU admission.[54] Daily organ failure status was measured via Sequential Organ Failure Assessment (SOFA) score.[55] Daily mechanical ventilation status, fraction of inspired oxygen (FiO_2), and positive end-expiratory pressure (PEEP) data were collected from morning ventilator settings. Daily benzodiazepine and opioid infusion status were measured in addition to daily morning sedation and delirium status using the Richmond Agitation Sedation Scale (RASS) [56] and CAM-ICU,[57] respectively. Patient sedation status was qualitatively classified as follows: awake (RASS ≥ -1), lightly sedated (RASS -2 or -3) or deeply sedated/comatose (RASS -4 or -5).

Statistical analyses

Patient and ICU-related variables were compared between the pre-QI and post-QI groups using Pearson's chi-square, Fisher's exact, or Wilcoxon rank-sum tests as appropriate. Sedation and delirium assessments were not completed as part of routine care in the pre-QI period, but completed by study

staff. Hence, missing data (e.g. due to lack of staff coverage on weekends or during holidays) were imputed using multiple imputation[58] (with five datasets) as described elsewhere.[59]

We compared time to initiation of active physical therapy intervention for patients admitted to the MICU during the post-QI versus pre-QI periods. Bivariable associations of patient and ICU-related variables with time to initiation of active physical therapy intervention were evaluated using Fine and Gray proportional sub-distribution hazards regression analysis. The Fine and Gray method was used to account for the competing risk of mortality while analyzing associations of patient and ICU characteristics with the time to first physical therapy intervention.[60] To evaluate for violations of the proportionality assumption in the regression analysis, Schoenfeld residuals were plotted versus functions of time.[61] Covariates with a bivariable association with time to first physical therapy intervention of $p<0.150$ were included in the multivariable Fine and Gray regression model.

Multicollinearity was assessed in the multivariable regression model using variance inflation factors.[62] This analysis demonstrated that daily delirium status was strongly collinear with daily sedation status, and therefore delirium status was excluded from the final regression model. Cumulative incidence function curves were created by first fitting the final multivariable regression model to each of the five imputed sedation status datasets and obtaining the average cumulative incidence of initiation of active physical therapy intervention.

We assessed for statistical interaction between admission during the post-QI period and the following clinically relevant covariates based on *a priori* hypotheses: age, BMI, APACHE II score, SOFA score, mechanical ventilation status, FiO_2, PEEP, and sedation status. Statistical analyses were performed using STATA 12.0 software (Stata Corporation, College Station, TX). Statistical significance was defined as a two-sided $p<0.05$. The institutional review board at Johns Hopkins University approved this evaluation.

Results

Patients in the pre-QI (n=120) versus post-QI (n=123) periods were similar in most demographic and ICU-related variables (Table 1). Across the entire patient cohort (n=243), 52% were female, with a median (inter-quartile range [IQR]) age and APACHE II score of 49 [40 – 59] years and 29 [24, 35], respectively. Moreover, among all patients, 92% had a PaO2/FiO2 <200 (46% had PaO2/FiO2 <100) at ALI onset, and a median [IQR] daily average PEEP of 6.9 cmH2O [5.0, 9.3]. ICU mortality was 45% (not significantly different in post-QI versus pre-QI: 41% versus 48%, p=0.282). In the post-QI versus pre-QI period, patients were more frequently admitted from an outside hospital (34% vs. 18%), and patients were less sedated with a higher median [IQR] daily average RASS score (-2.1[-3.5,-1.0] vs. -3.2[-4.3,-2.4], p<0.001) and lower median [IQR] proportion of ICU days on a benzodiazepine infusion (50% [0,100] vs. 72% [49,100], p<0.001) and with deep sedation/coma (33% [0,70] vs. 60% [38,88], p<0.001).

Among all patients, 68% in post-QI and 16% in pre-QI group ever received physical therapy (Table 2). Moreover, those in the post-QI versus pre-QI group had a shorter median [IQR] time to first physical therapy intervention (4 [2,6] vs. 11 [6,29] days, p<0.001), greater median [IQR] proportion of ICU days with physical therapy after its initiation (50% [33,67] vs. 18% [4,47], p=0.003), and a greater proportion of patients achieving a highest daily activity level of standing, transferring and/or ambulating during physical therapy treatment in the ICU (41% vs. 4%, p<0.001) (Table 2). When restricting analyses to those surviving until ICU discharge, the median [IQR] time to first physical therapy intervention remained shorter in the post-QI versus pre-QI group (4 [2,6] vs. 12 [6.29], p<0.001), and an even greater proportion of patients in the post-QI versus pre-QI group ever received physical therapy in the ICU (89% vs. 24%, p<0.001) and achieved a highest daily activity level of standing, transferring and/or ambulating in the ICU (64% vs. 7%, p<0.001). There were no prospectively recorded physiological abnormalities or potential safety events in the post-QI group (Table 2).

In regression analysis, the post-QI period was independently associated with a shorter time to initiation of active physical therapy intervention (adjusted hazard ratio (HR) [95% CI]: 8.38 [4.98, 14.11], p<0.001) (Table 3) (Figure 1). In a post-hoc analysis, this association with a shorter time to physical therapy was similar for each year within the 5-year post-QI period. Among ICU-related variables (analyzed as time-varying daily exposures), the following were significantly associated with longer time to initiation of active physical therapy intervention (adjusted HR, [95% CI]): higher SOFA score (0.93 [0.89, 0.97], p<0.001), higher FiO2 (0.86 [0.75, 0.99] for a 10% increase, p=0.038), any opioid infusion (0.47 [0.25, 0.89], p=0.021), and deep sedation/coma (0.24 [0.12, 0.46], p<0.001). None of the *a priori* selected exposures (BMI, APACHE II score, SOFA score, mechanical ventilation status, FiO_2, PEEP, and sedation status) had any significant statistical interaction with the post-QI (vs. pre-QI) period and its association with timing of initiation of active physical therapy intervention in the ICU.

Discussion

In this single site, pre-post evaluation of 243 patients predominantly with moderate or severe ALI, an early rehabilitation QI project was independently associated with a large and statistically significant decrease in the time to initiation of active physical therapy intervention, and this association was sustained for 5 years after completion of the QI project. There was no modification of the association between admission during the post-QI period and earlier initiation of active physical therapy intervention by any patient or ICU-related factors. Increased severity of illness and hypoxia, any opioid infusion and deep sedation were independently associated with delayed initiation of active physical therapy intervention in the MICU.

To our knowledge, this is the first report of the sustainability of an ICU-based early rehabilitation QI project. Similar to prior publications on the implementation of successful QI projects, our MICU underwent a substantial culture change to engage the multidisciplinary team in promoting and

executing the QI project.[26] This culture change included education on the importance and success of early rehabilitation in the ICU, implementation of simple guidelines to ensure safe and timely referral to PT, and improved multidisciplinary communication and clinical care. This report is novel because it demonstrates these changes can be incorporated into routine clinical practice across more than 20 physical therapists providing clinical care in the MICU, thereby contributing to successfully sustaining early rehabilitation long after completion of a QI project.

The time to initiation of active physical therapy intervention was significantly shorter in the post- versus pre-QI period (4 vs. 11 days) but longer than the 1.5 days reported in a randomized controlled trial (RCT) of 104 mechanically ventilated MICU patients.[14] There are important distinctions between these two study designs that may account for this difference. The general aim of RCTs is to establish efficacy of an intervention, typically in the context of a resource-intensive research environment with a highly selected subset of consenting patients. These circumstances may not reflect routine clinical practice that is evaluated in quality improvement projects.[42,63] For instance, in our evaluation versus the RCT, patients without baseline functional independence were not excluded and severity of illness was substantially higher as reflected by median APACHE II scores (29 vs. 20) and proportion of participants with moderate or severe ALI (92% versus 55%).

Of those surviving until ICU discharge, 89% of patients in the post-QI group received physical therapy in the ICU, similar to the previously described RCT, in which 94% (46/49) of patients received physical therapy and occupational therapy in the ICU.[14] Likewise, in another evaluation of an early mobility protocol including 116 mechanically ventilated MICU patients, 91% received physical therapy in the ICU.[19] Among patients in the pre-QI control period in our evaluation, 16% ever received physical therapy in the ICU and 4% were mobilized out of bed. These findings are similar to other evaluations of routine ICU care. For instance, in a one day point prevalence study including 783 patients in 116 ICUs in

Germany, 8% of patients with an endotracheal tube were mobilized out of bed.[25] Moreover, in another point prevalence study of 514 patients in 38 New Zealand and Australian hospitals, no mechanically ventilated patients were mobilized out of bed.[23] Finally, the control groups of ICU rehabilitation studies of mechanically ventilated patients[22] have demonstrated that 13% of mechanically patients received physical therapy in the ICU[19] and the median (IQR) duration of PT and OT in the ICU was 0 (0, 0) minutes.[14]

Two non-modifiable risk factors, severity of organ failure and hypoxia, were associated with delayed initiation of physical therapy. In prior studies, increased organ failure[24,64] and physiologic instability[25] were associated with delayed initiation of physical therapy, and respiratory instability also has been as a barrier to early mobilization.[21] Importantly, despite a high severity of illness in the post-QI patients, early physical therapy was initiated without the occurrence of any prospectively-evaluated and defined major physiological abnormalities or potential safety events. These findings support existing literature demonstrating the safety of early rehabilitation in critically ill patients.[12-14,18,19,23,37,38]

In our analysis, there were two modifiable risk factors independently associated with delayed initiation of physical therapy: deep sedation and receiving an opioid infusion. Sedation is a known barrier to physical therapy in critically ill patients.[16,21,25] In the current study, a sedation protocol was implemented coincident with the early rehabilitation program in order to reduce this modifiable barrier to physical therapy.[45] Such pairing of an early rehabilitation program with a sedation protocol is common in other studies of ICU rehabilitation interventions.[14,28,65] Despite adjusting for differences in sedation practice between pre- and post-QI periods, admission during the post-QI period remained significantly associated with earlier initiation of physical therapy.

There are possible limitations to this study. Because this was an observational pre-post evaluation, we cannot prove causation between the patient and ICU-related variables evaluated and

time to initiation of physical therapy, and residual confounding may influence the results. Nonetheless, our findings are consistent with prior RCTs evaluating early rehabilitation in critically ill patients[14,18] and reports of barriers to mobilization.[13,16,17,21] Moreover, the study population consisted solely of ALI patients in an adult MICU within a single academic hospital. Therefore, the findings may not be generalizable to other populations and settings. However, ALI patients are the archetype of severely critically ill patients; thus, supporting the generalizability of our findings to populations with a similar or lesser severity of illness.[19,29-36]

In conclusion, an early rehabilitation QI project was independently associated with a substantial decrease in the time to initiation of physical therapy intervention that was sustained for five years after project completion. The association between the post-QI rehabilitation program and earlier initiation of physical therapy was not modified by patient-related or ICU-specific factors. Modifiable factors independently associated with delayed initiation of physical therapy included opioid infusions and deep sedation, while severity of organ failure and hypoxia were non-modifiable patient risk factors for delayed initiation. These findings may help inform new and existing rehabilitation programs regarding the possibility for sustainable benefits of structured quality improvement projects.

Chapter 4 – Section A Reference List

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Chapter 4 – Section A Tables

Table 1. Baseline characteristics[a]

	All[b, c] (n=243)	Pre-QI (n=120)	Post-QI (n=123)	p-value[d]
Age, median (IQR), years	49 (40, 59)	48 (40, 57)	51 (37, 63)	0.163
Female, n (%)	127 (52)	57 (47)	70 (57)	0.142
White race, n (%)	106 (44)	47 (39)	59 (48)	0.167
BMI, median (IQR)	26 (22, 32)	27 (23, 32)	26 (22, 32)	0.601
BMI ≥30, n (%)	97 (40)	43 (36)	54 (44)	0.238
Charlson comorbidity index, median (IQR)	2 (1, 4)	3 (1, 5)	2 (0, 4)	<0.001
Functional comorbidity index, median (IQR)	1 (1, 3)	1 (1, 2)	1 (1, 3)	0.164
ICU admission source, n (%)				0.025
Emergency room	63 (26)	33 (28)	30 (24)	
Ward	106 (44)	61 (51)	45 (37)	
Other ICU	10 (4)	4 (3)	6 (5)	
Other hospital	64 (26)	22 (18)	42 (34)	
ICU admission diagnosis, n (%)				0.069
Respiratory (including pneumonia)	149 (61)	80 (67)	69 (56)	
Sepsis/infectious disease	47 (19)	18 (15)	29 (24)	
Gastrointestinal	25 (10)	14 (12)	11 (9)	
Cardiovascular	6 (2)	4 (3)	2 (2)	
Central nervous system	4 (2)	2 (2)	2 (2)	
Other	12 (5)	2 (2)	10 (8)	
APACHE II at ICU admission, median (IQR)	29 (24, 35)	29 (23, 36)	29 (25, 35)	0.906
SOFA-Respiratory score Day 1, median (IQR)	3 (3, 4)	4 (3, 4)	3 (3, 4)	0.079
PaO_2/FiO_2 on Day 1, n (%)				0.109
≥200	20 (8)	10 (9)	10 (9)	
≥ 100 & <200	105 (46)	46 (39)	59 (52)	
<100	105 (46)	61 (52)	44 (39)	
Mean daily SOFA score, median (IQR)	10 (6 ,14)	10 (6, 15)	10 (7, 13)	0.980
Proportion of ICU days on mechanical ventilation, median (IQR)	83 (67, 95)	80 (67, 91)	86 (67, 100)	0.047
Average FiO_2, median (IQR)	54 (44 ,67)	52 (43, 63)	56 (47, 68)	0.065
Average PEEP, median (IQR)	6.9 (5.0, 9.3)	6.7 (5.0, 9.3)	7.3 (5.0, 9.3)	0.322
Proportion of ICU days on benzodiazepine infusion, median (IQR)	60 (29, 100)	72 (49, 100)	50 (0, 100)	<0.001
Proportion of ICU days on opioid infusion, median (IQR)	74 (39, 100)	80 (50, 100)	67 (14 ,100)	0.056
Average RASS, median (IQR)[e]	-2.9 (-3.9, -1.7)	-3.2 (-4.3, -2.4)	-2.1 (-3.5, -1.0)	0.001
Proportion of ICU days, median (IQR)[e]				
Awake	26 (0, 50)	21 (2, 40)	33 (0, 67)	0.093
Lightly sedated	14 (0, 32)	11 (0, 26)	20 (0, 35)	0.334

Deeply sedated/comatose	51 (17, 81)	60 (38, 88)	33 (0, 70)	<0.001
Proportion of ICU days with delirium, median (IQR)[e]	32 (10, 56)	25 (9, 42)	43 (17, 75)	0.008

Abbreviations: QI, quality improvement; IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; PaO_2, arterial partial pressure of oxygen;FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation Sedation Scale

[a]Percentages may not equal 100 due to rounding.

[b]All time-varying data, except when indicated as Day 1 of acute lung injury (ALI), are from date of ALI to date of first PT or ICU discharge.

[c]Missing Data pre-QI/post-QI: BMI 2/20; Day 1 Sofa Respiratory Score (P/F) 3/10; FiO2 1/6; PEEP 1/9; RASS 0/3

[d]Comparing pre-QI and post-QI groups and calculated using Pearson's chi-square, Fisher's exact, and Wilcoxon rank-sum tests, as appropriate

[e]Patient sedation status was classified as follows: awake (RASS ≥ -1), lightly sedated (RASS -2 or -3) or deeply sedated/comatose (RASS -4 or -5). Five imputed datasets were used to address missing data for RASS and CAM-ICU in the pre-QI group; the data presented represents the mean value for the median (IQR) of the 5 datasets using a pooled Z-score to obtain the p-values.[66]

Table 2. **Active physical therapy intervention in the medical intensive care unit, before and after a quality improvement project**

	Pre-QI (n=120)	Post-QI (n=123)	p-value[a]
Ever receiving active PT intervention, n (%)	19 (16)	84 (68)	<0.001
Days to first active PT intervention, median (IQR)	11 (6, 29)	4 (2, 6)	<0.001
Number of PT sessions in index MICU admission, median (IQR)	0 (0, 0)	3 (0, 5)	<0.001
Percent ICU days with PT session, median (IQR)	0 (0, 0)	23 (0, 43)	<0.001
Percent ICU days with PT session after initiation, median (IQR)	18 (4, 47)	50 (33, 67)	0.003
Physiological abnormality or potential safety events, n (percent of PT treatment sessions) [b]	--	0 (0%)	N/A
Highest daily activity during PT session during ICU stay, n (%)			<0.001
Lying or sitting in bed	113 (94)	60 (49)	
Sitting at edge of bed	3 (3)	13 (11)	
Standing or transfer to chair	3 (3)	28 (23)	
Walking	1 (1)	22 (18)	

Abbreviations: ICU, intensive care unit; QI, quality improvement; PT, physical therapy; IQR, inter-quartile range; ICU, intensive care unit

[a] Calculated using Pearson's chi-square, Fisher's exact, and Wilcoxon rank-sum tests, as appropriate

[b] Safety events were not collected for the Pre-QI period. Safety events were prospectively collected during the post-QI period and defined as any of the following: (1) removal, dislodgment, disruption, or dysfunction of airway, feeding tube, chest tube, vascular access, cardiac device, or wound dressing; (2) cardiovascular/hemodynamic instability that includes hyper- and hypotension, desaturation, cardiac arrest, arrhythmia, and death; or (3) falls.[37]

Table 3: Factors associated with time to initiating physical therapy in the medical intensive care unit

	Unadjusted[a]			Adjusted[a]		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age, years	1.00	0.99 – 1.02	0.523			
Male	0.90	0.62 – 1.31	0.576			
White (versus non-white)	1.33	0.92 – 1.93	0.134	1.14	0.78 – 1.68	0.496
BMI ≥30 kg/m^2	0.68	0.46 – 1.02	0.059	0.71	0.48 – 1.06	0.096
Charlson comorbidity index	0.91	0.83 – 0.98	0.020	0.97	0.91 – 1.04	0.400
Functional comorbidity index	1.04	0.93 – 1.16	0.471			
Admission during early rehabilitation	7.03	4.40 – 11.22	<0.001	8.38	4.98 – 14.11	<0.001
Source of ICU admission						
Emergency room	1.00					
Ward	1.02	0.63 – 1.65	0.945			
Other ICU	1.34	0.54 – 3.32	0.525			
Other hospital	1.28	0.76 – 2.14	0.351			
ICU admission diagnosis						
Respiratory (including pneumonia)	1.00					
Sepsis/infectious disease	0.84	0.53 – 1.33	0.453			
Gastrointestinal	0.56	0.28 – 1.11	0.096			
Cardiovascular	0.37	0.05 – 2.56	0.311			
Central nervous system	1.33	0.29 – 6.22	0.714			
Other	1.64	0.70 – 3.83	0.256			
APACHE II at ICU admission	0.98	0.96 – 1.00	0.088	0.99	0.97 – 1.02	0.595
Daily SOFA score	0.90	0.87 – 0.93	<0.001	0.93	0.89 – 0.97	0.001
Daily mechanical ventilation status	0.34	0.20 – 0.58	<0.001	0.83	0.41 – 1.71	0.614
FiO_2 received (every 10% increase)	0.69	0.62 – 0.78	<0.001	0.86	0.75 – 0.99	0.038

	Unadjusted[a]			Adjusted[a]		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
PEEP	0.86	0.82 – 0.90	<0.001	0.99	0.91 – 1.08	0.812
Benzodiazepine infusion	0.23	0.15 – 0.35	<0.001	0.90	0.44 – 1.86	0.778
Opioid infusion	0.25	0.16 – 0.37	<0.001	0.47	0.25 – 0.89	0.021
Sedation Status[b]						
Awake	1.00			1.00		
Light sedation	0.56	0.27 – 1.16	0.109	0.66	0.41 – 1.04	0.077
Deep sedation/Comatose	0.09	0.05 – 0.17	<0.001	0.24	0.12 – 0.46	<0.001

Abbreviations: ICU, intensive care unit ; CI, confidence interval; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure

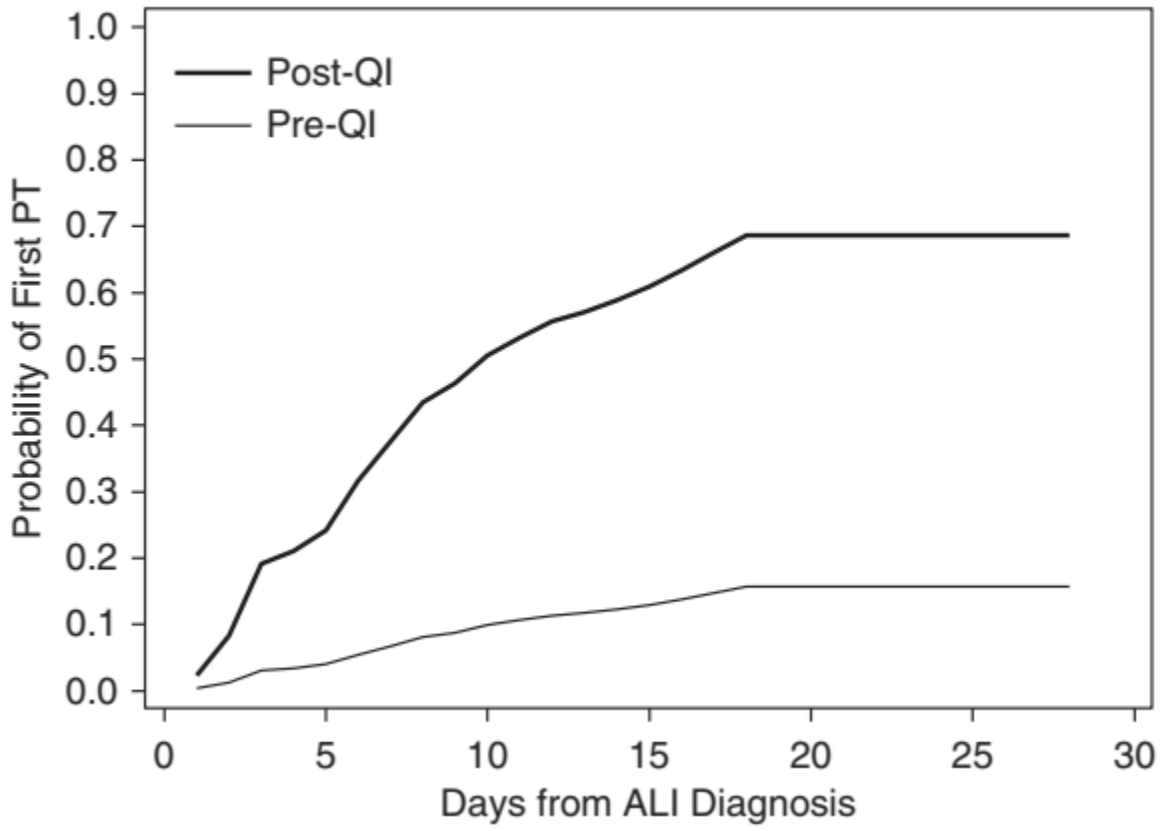
[a]Hazard ratios greater than 1 indicate an association with earlier initiation of active physical therapy in the MICU. Hazard ratios were calculated using Fine and Gray regression models,[60] with daily time-varying exposures for SOFA score, mechanical ventilation status, FiO_2, PEEP, benzodiazepine infusion, opioid infusion, and sedation status.

[b]Patient sedation status was classified as follows: awake (RASS ≥ -1), lightly sedated (RASS -2 or -3) or deeply sedated/comatose (RASS -4 or -5).

Chapter 4 – Section A Figures

Legends:

Figure 1. Probability of active physical therapy intervention in the medical intensive care unit in the pre-quality improvement versus post-quality improvement period[a].



Abbreviations: QI, quality improvement; PT, physical therapy; ALI, acute lung injury.
[a]Estimates are adjusted for all variables included in the multivariable regression model presented in Table 3.

CHAPTER 4

SECTION B

Cognitive Stimulation in a Medical Intensive Care Unit: A Qualitative Evaluation of Barriers and Facilitators to Implementation

Ann M. Parker, MD[1,3], Louay Aldabain, MD[2,3], Narges Akhlaghi, MD[3], Mary Glover, MSN, RN, CCRN[4], Stephanie Yost, BSN, RN[4], Michael Velaetis, PA[4], Annette Lavezza, OTR/L[5], Earl Mantheiy, BA[1,3], Kelsey Albert, BA[1,3], and Dale M. Needham, FCPA, MD, PhD[1,3,6]

[1] Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2] MedStar Union Memorial Hospital, Baltimore, MD, USA

[3] Outcomes After Critical Illness and Surgery (OACIS) Group, Johns Hopkins University, Baltimore, MD, USA

[4] Medical Intensive Care Unit, Johns Hopkins Hospital, Baltimore, MD, USA

[5] Department of Physical Medicine and Rehabilitation, Johns Hopkins Hospital, Baltimore, MD, USA

[6] Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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Abstract

Background: Guidelines support non-pharmacologic management, including cognitive stimulation, to address intensive care unit (ICU) delirium.

Objectives: To qualitatively evaluate barriers and facilitators to cognitive stimulation, as part of a structured quality improvement (QI) project, in a medical ICU (MICU).

Methods: Themes arising from semi-structured interviews with MICU nurses were categorized using the Consolidated Framework for Implementation Research (CFIR).

Results: Twenty-three MICU nurses identified 62 barriers to cognitive stimulation and 26 facilitators. The resulting 12 barrier and 9 facilitator themes corresponded to the CFIR domains: Intervention Characteristics, Outer Setting, Inner Setting, Characteristics of Individuals, and Process. Patient-specific variables (e.g. sedation) were most frequently reported. Other barriers included: cognitive stimulation not a priority; nurse staff barriers; documentation burden; and lack of appreciation for evidence supporting cognitive stimulation.

Conclusions: Barriers to cognitive stimulation in the MICU arise from the organization, context and individuals associated with the intervention as well as the intervention itself.

Introduction

Delirium occurs in up to 80% of mechanically ventilated and 50% of non-mechanically ventilated patients during their intensive care unit (ICU) stay.[1] In these patients, delirium is associated with worse outcomes, including increased duration of mechanical ventilation and length of stay[2-6] and greater cognitive impairment at one year after discharge.[7,8] Hence, the prevention and treatment of delirium is important to improve outcomes for critically ill patients.

Several recent studies have shown no benefit of pharmacologic therapy in preventing or treating delirium in critically ill patients,[9-11] and the recently updated Society of Critical Care Medicine (SCCM) "Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption" (SCCM PADIS Guidelines) do not support the routine use of antipsychotics to manage delirium in the ICU. However, the guidelines do support the use of multi-component, non-pharmacologic interventions, including cognitive stimulation, to manage delirium.[12]

A pilot randomized controlled trial (RCT) in 140 non-mechanically ventilated ICU patients demonstrated that an early occupational therapy (OT) intervention (vs. usual care) decreased the incidence of delirium (3% vs. 20%, $p< 0.001$) and the proportion of study days with delirium (1% vs. 8%).[13] Early OT involved two 40-minute sessions each day of a multi-component intervention including cognitive stimulation, which consisted of a notebook with tasks aimed at activating mental functions (e.g. alertness, visual perception, problem solving, etc).[13] Meta-analyses have demonstrated that similar, multi-component non-pharmacologic delirium interventions are consistently associated with decreased incidence of delirium in both general medical/surgical and critically ill patients.[14,15] Inspired by these studies, we commenced a structured quality improvement (QI) project to introduce cognitive stimulation, performed by nurses, in the [site de-identified] Hospital medical intensive care unit (MICU).

Understanding barriers to implementation is an essential component of translating evidence into practice.[16] Therefore, the current project aimed to evaluate, using qualitative methods, potential barriers and facilitators to implementation of a cognitive stimulation intervention in an academic MICU in North America.

Methods:

QI project and planning

Starting in September 2017, a QI project was undertaken to implement combined cognitive stimulation and early, goal-directed mobility, performed by nurses, in the [site de-identified] MICU. Notably, the [site de-identified] MICU had already incorporated many aspects of the above-mentioned multi-component pharmacologic interventions, including early physical and occupational therapy, sedation protocol and reorientation, into routine care based on existing evidence. With the emergence of newer evidence,[12-14] the decision was made to include cognitive stimulation as well. The planning and preparation for the MICU QI project (which is currently on-going) started in November 2016 and included establishment of a multidisciplinary team (including nurses, advanced practice providers, physicians, clinical technicians, physical and occupational therapists, and respiratory therapists). This project was reviewed by the [site de-identified] Institutional Review Board and was designated as quality improvement with a waiver of consent.

Cognitive stimulation consisted of nurses reviewing a workbook of evidence-based tasks (focused on "alertness, visual perception, memory, calculus, problem solving, praxis, and language")[13] with patients (Richmond Agitation Sedation Scale Score -2 to +2) to reduce the incidence and duration of delirium in critically ill patients. While in a prior study cognitive stimulation was implemented by occupational therapists,[13] nurses were chosen to implement cognitive stimulation as part of this QI project on a daily

basis as part of routine care. Preparation for the QI project included establishment of seven nursing super-users who then educated and trained the nursing staff on administration and then documentation of cognitive stimulation in the electronic medical record (EMR) using the following options: yes, no or not applicable. Approximately three months after launching the QI project, documentation of cognitive stimulation was noted to be low (~30%), thus making it challenging to infer implementation rate as well. Therefore, the multi-disciplinary QI team decided to qualitatively evaluate the potential barriers to nurse-driven cognitive stimulation by conducting semi-structured interviews with MICU nurses.

Development of Interview Guide

The interview guide was initially developed by a member of the QI team (AMP) with expertise in qualitative research, and then reviewed and revised with input from all members of the multidisciplinary quality improvement team before any nurses were approached. The final interview guide consisted of 5 questions (Table 1) with probing, as needed, and based on the judgment of the interviewers.

Interview process

Beginning in October 2018 and continuing into December 2018, using purposive sampling, the interviewer approached bedside nurses. Day shift nurses were approached in the mid-afternoon while night shift nurses were approached about one hour before shift change in order to avoid the busiest times of the shift. Interviews took place in the MICU either at the work desk outside of patient rooms or at the nursing stations. The initial four interviews were conducted by a physician member of the team (AMP) who then trained an additional physician (LA) to assist with the remaining interviews. In order to encourage nurses to respond openly about perceived barriers, 1) physician members of the QI team were selected to conduct the interviews since they were not direct nursing supervisors, and 2) the interviews were not audio-recorded. Thus, nurse feedback (Results section) is not necessarily

transcribed verbatim. Instead, interviewers recorded detailed field notes, including nurses' responses to questions, points of clarification, interviewer reflection on nurses' responses and any other details that were perceived as potentially relevant.

Coding and Development of Themes

Initially, nurses were asked questions regarding barriers to implementation of cognitive stimulation in the MICU. However, many nurses also discussed facilitators, and so the codebook included both barriers and facilitators to cognitive stimulation implementation. Coding was conducted by a member of the QI team (AMP) with expertise in qualitative research methods who then trained two additional reviewers (LA and NA) and performed quality assurance. Using thematic analysis, two reviewers (LA and NA) independently read the field notes line by line to inductively create a codebook.[17-19] For the initial round of coding, the second coder coded the first seven interviews in reverse order. After coding the first seven interviews, three team members (AMP, LA, NA) met in person to evaluate for the emergence of themes. Interviews continued with concurrent coding by two independent reviewers (LA and NA) with discrepancies resolved by a third reviewer (AMP). After every three to five interviews, the codebook was updated and reviewed for potential coding saturation. Coding saturation was achieved after 20 interviews, and three more interviews were conducted to confirm coding saturation, with a total of 23 interviews completed. The codebook was then updated and reviewed by all three reviewers to confirm completeness. Two independent reviewers (LA and NA) then independently coded each transcript with a third reviewer resolving discrepancies (AMP). The barriers and facilitators were summarized into themes which were subsequently mapped using the Consolidated Framework for Implementation Research (CFIR), a set of constructs that allow for systematic and comprehensive evaluation of implementation.[15] The five CFIR domains include: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation (Appendix: eTable 1).[20] These themes were

confirmed for completeness and accuracy with three MICU nurses as a means of member checking, a strategy used to evaluate the reliability of qualitative data.[21] Three independent reviewers (LA, NA, AMP) assigned each barrier to a CFIR construct, with discrepancies resolved by group consensus. This qualitative project is reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ) (Appendix: eTable 2).[22]

Results:

Respondent Characteristics

Interviews were conducted with 23 MICU nurses. All nurses agreed to participate. Seventeen (74%) of the nurses interviewed were women, and 12 nurses (61%) were on day shift at the time of the interview. Nurses had been in the profession for a mean (standard deviation (SD)) of 9 (9) years and working in the [site de-identified] MICU for 6 (7) years. Each 5-question semi-structured interview took up to ten minutes to complete.

Twenty-two out of 23 (96%) nurses were aware of the QI project and had attempted cognitive stimulation with at least one patient and identified multiple barriers to cognitive stimulation in the MICU. Nineteen (83%) nurses identified at least one facilitator for implementation of cognitive stimulation in the MICU.

Descriptions of Barriers and Facilitators

Nurses identified a total of 62 barriers to cognitive stimulation implementation as well as 26 facilitators. These were further summarized into 12 barrier (Table 2) and 9 facilitator (Table 3) themes that were subsequently mapped to the CFIR domains and constructs. Exemplar statements are reported in Tables 4 and 5.

CFIR Intervention Characteristics

Ten nurses (43%) reported that the current method (free-text entry) for documentation of cognitive stimulation in the EMR was a barrier to implementation. Nurses stated that having a designated section in the EMR that included drop-down lists would facilitate implementation.

Some nurses commented on the adaptability of the cognitive stimulation intervention, suggesting it might be more appealing to some patients if it could be delivered via an electronic tablet. Similarly, nurses believed the intervention could be improved by translating it into other languages for use by non-English-speaking patients.

CFIR Outer Setting

Patient-specific variables were the most frequently reported barriers to cognitive stimulation (reported by 20 nurses (87%)). Nurses stated that some patients were not cooperative with cognitive stimulation because they did not like the workbook or due to sedation, pain, agitation, or fatigue. Among these, sedation was the most commonly cited barrier. While some nurses described apprehension over even offering the packet because of perceived patient opposition, others said that patients clearly declined to participate in cognitive stimulation. One nurse described that while she was sometimes concerned she might offend patients by asking them to complete the relatively simple tasks, she would address this potential barrier by explaining the reasoning for cognitive stimulation to patients who were reluctant to do the tasks.

Nurses also pointed out that cognitive stimulation using the packet could be more challenging for patients who were non-English speaking or hearing or vision impaired or had difficulty using their hands. At least one nurse described lack of family support for cognitive stimulation.

CFIR Inner Setting

Seventeen (74%) nurses reported that the current MICU climate did not support cognitive stimulation as a relative priority. For example, one nurse reported: *Sometimes it feels it's less of a priority than other tasks, especially in the ICU.* Similarly, night shift nurses believed patients' sleep was a priority and thus, cognitive stimulation should be administered during day shift only. Nurses also referred to staff barriers to implementing cognitive stimulation, including the overall workload, staff turnover and lack of patient continuity. A representative statement was: *Any task that doesn't have specialists falls on nurses.* Overall burden of documentation was also cited as a barrier to implementation of cognitive stimulation.

Other nurses felt the MICU culture was one that supported QI projects or research focused on improving patient care and described how this culture facilitated implementation of cognitive stimulation. These nurses often compared the current QI project involving cognitive stimulation to a prior structured QI project in the same MICU that focused on reducing sedation and delirium.[18]

Packet availability was also a barrier to implementation with nurses reporting that packets were unusable or sometimes missing from patient rooms altogether.

CFIR Characteristics of Individuals

Ten (43%) nurses described an incomplete understanding of the evidence supporting cognitive stimulation to prevent and treat delirium in critically ill patients and cited this as a barrier to

implementation. Moreover, some nurses were reluctant to engage patients perceived as having no cognitive impairment in cognitive stimulation because they worried such patients would be offended by what the nurses perceived as simple task. Other nurses reported that their appreciation for the benefits of cognitive stimulation and the importance of preventing and treating delirium motivated their efforts to engage patients in cognitive stimulation. Only two nurses acknowledged lack of familiarity with the packet, especially among new or travel nurses, as a barrier to administering cognitive stimulation.

CFIR Process

While there were no barriers to cognitive stimulation identified within the CFIR domain "Process", nurses did suggest several potential facilitators within this domain. Nurses frequently referred to existing multidisciplinary education and training regarding administration and documentation of cognitive stimulation as facilitators for implementation. Some nurses stated more training was needed and suggested a process for periodic re-education. Moreover, at least one nurse felt it would be helpful to train families to assist with cognitive stimulation.

Nurses had several ideas regarding incorporation of cognitive stimulation into their daily workflow (Table 3). Nurses suggested administering cognitive stimulation and completing the documentation along with assessments of cognition, including the Confusion Assessment Method for the ICU (CAM-ICU)[23] and Richmond Agitation-Sedation Scale (RASS).[24]

Nurses reported that reminders to administer and document cognitive stimulation facilitated implementation. These reminders included a prompt during each shift via the unit phones carried by all nurses.

Results of Member Checking

Overall, three nurses agreed that the barrier and facilitator themes were representative of the nurses' thoughts regarding cognitive stimulation. They emphasized the overall desire for more autonomy in delivery of the intervention, including via the addition of more complicated tasks for patients who were cognitively intact and the option to use an electronic tablet to administer cognitive stimulation (see CFIR Process above and Table 3).

Discussion:

Through this qualitative project evaluating implementation of cognitive stimulation in an academic MICU in North America, nurses identified 62 barriers and 26 facilitators which could be summarized into 12 barrier and 9 facilitator themes corresponding to each of the CFIR domains. Barrier and facilitator themes arose from the organization, context and individuals associated with the intervention as well as the intervention itself, while nurses identified potential facilitators within the implementation process ("engaging").

Identifying barriers to implementation is an important step in the QI process,[16] and a critical aspect of intervention implementation. The most commonly cited barriers to cognitive stimulation were patients declining or lack of cooperation due to sedation, pain, agitation, fatigue or disinterest and fell within the CFIR domain "outer setting" and the construct "patient needs and resources".[20] Sedation was the most frequently cited reason for patients' inability to cooperate with cognitive stimulation. This is consistent with evaluations of barriers to other ICU-based interventions, including early mobility and delirium assessments. A systematic review, including 40 studies, identified "patient-related" barriers as the most commonly reported barriers to early mobilization of critically ill patients, and among these, sedation was reported the most frequently.[25] Similarly, a study evaluating ICU nurses' practices and perceptions

regarding delirium assessments, using a survey administered to 331 nurses demonstrated that sedation was one of the more commonly reported barriers to delirium assessment.[26] Sedation might be an appropriate contraindication to cognitive stimulation as some patients require deep sedation for severe acute respiratory distress syndrome or other medical conditions. However, in other instances, there might be an opportunity for improved sedation practices, similar to those first fostered by a structured QI project in the [site de-identified] MICU, which aimed to decrease sedation and delirium using a sedation protocol and was indeed associated with increased wakefulness.[27]

Another frequently reported barrier, corresponding to the CFIR domain "characteristics of individuals" and construct "knowledge and beliefs about the intervention", involved nurses' perception of some patients as cognitively intact (or not delirious) and thus not likely to benefit from cognitive stimulation. This raises two important issues regarding the management of delirium in ICU patients. First, delirium and associated cognitive impairment is substantially under-recognized in the ICU by nurses and physicians. A study following 46 patients over 425 patient days, using the CAM-ICU as the reference standard for delirium assessment, showed that nurses and physicians detected only 35% and 28% of delirium-days, respectively.[28] Second, cognitive stimulation may *prevent* the development of delirium in critically ill patients who appear otherwise cognitively intact,[13] and primary prevention is likely the most effective strategy for reducing the complications associated with delirium.[29] Indeed, in a study of over 800 older hospitalized patients, a multicomponent intervention was successful in preventing delirium, but once delirium occurred, the intervention did not improve the severity of delirium or the likelihood of a subsequent episode.[29]

Nurses identified several facilitators within the CFIR domain "process" and construct "engaging". First, nurses acknowledged the existing training and education that were part of the QI project planning and

preparation but felt more was needed. The QI team responded by presenting the evidence for cognitive stimulation as well as the QI project progress at MICU staff meetings and identifying a dedicated MICU occupational therapist who engaged the nurses in additional training. Moreover, nurse members (MG, SY) of the QI team incorporated the following education into the next round of super-user training: evidence supporting cognitive stimulation, creative ways to engage patients in cognitive stimulation, and proper documentation. The nurse super-users also conducted real-time audits and gave immediate feedback, which included further education as needed. This iterative approach to implementation, including sharing of evidence to support the intervention and feedback on performance measures, is an important but often overlooked aspect of translating evidence into practice.[16,20] Second, the nurses suggested several ways to incorporate cognitive stimulation into their daily workflow. As part of the QI planning process, members of the multidisciplinary QI team directly observed nurses who were found to have very little time for additional tasks.[30] Thus, incorporating cognitive stimulation into the nurses' patient care routine is essential for successful implementation. The most commonly suggested strategy for doing so was to administer and document cognitive stimulation with sedation (Richmond Agitation Sedation Scale) and delirium (CAM-ICU) assessments.

The nurses recognized the importance of culture change for successful implementation of an evidence-based intervention in the ICU as has been demonstrated for both implementation of early mobility[31] and recognizing and preventing delirium in the ICU.[32] The recently updated SCCM PADIS Guidelines support the use of multicomponent, non-pharmacologic interventions, including cognitive stimulation, as evidence-based strategies to manage delirium in the ICU.[12]

Our study had several limitations. First, there are several potential sources of bias in this qualitative evaluation. We attempted to maximize dependability by coding field notes and categorizing emerging

themes by at least two independent reviewers with discrepancies resolved by group consensus with a third independent reviewer. Also, in order to further assess the reliability of our data, we performed member checking whereby we elicited feedback on themes from several MICU nurses. Second, we interviewed a subset of nurses from a single ICU, and so the emergent themes might not represent the views of nurses in other units. However, the aim of this investigation was to identify barriers to cognitive stimulation within the setting of a structured QI project in the [site de-identified]. Third, interviews were conducted during nurses' shifts. However, interviewers offered to return during a more convenient time, if needed, and only one nurse requested the interviewer return during a less busy time. Moreover, the interviewers noted that nurses seemed eager to share their thoughts on the cognitive stimulation project. Finally, interviews were not recorded in order to maintain anonymity and encourage nurses to speak openly regarding their thoughts on the cognitive stimulation project. In place of transcribed interviews, interviews kept detailed field notes as described in the Methods Section.

Conclusion

Cognitive stimulation is an evidence-based method for delirium prevention. Implementation of cognitive stimulation requires addressing barriers that arise from attributes of the organization and context in which the intervention resides, the individuals involved, and the intervention itself.

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Chapter 4 – Section B Tables

Table 1. Interview Guide

1. What are your thoughts on the cognitive stimulation QI project that is currently occurring in the MICU?
2. What do you think are barriers to documenting whether or not the cognitive stimulation packet was reviewed with patients?
3. Probing: Can you give some examples of a time you did not document and why?
4. What do you think are barriers to reviewing the cognitive stimulation packet with patients?
5. Probing: Can you give some examples of a time you did not review with a patient and why?

Abbreviations: MICU = medical intensive care unit; QI = Quality Improvement

Table 2. Barriers to implementation of cognitive stimulation and the corresponding Consolidated Framework for Implementation Research domains and constructs

Domain: Intervention Characteristics Construct: Design Quality • Documentation - No designated section in electronic medical record
Domain: Outer Setting Construct: Patient Needs and Resources • Patient not cooperative/declines due to sedation, pain, agitation, fatigue, disinterest • Communication barriers (not English-speaking, visual or hearing impairment, restraints) • Family does not support cognitive stimulation
Domain: Inner Setting Construct: Relative Priority • Cognitive stimulation not a priority Construct: Implementation Climate • Night shift not perceived as the appropriate time to do cognitive stimulation Construct: Structural Characteristics • Nurse staff barriers (workload, staff turnover, lack of patient continuity) Construct: Available Resources • Burden of documentation • Packet Availability
Domain: Characteristics of Individuals Construct: Knowledge and Beliefs about the Intervention • Lack of understanding of, or appreciation for, evidence for cognitive stimulation • Nurse perceives that patient will be offended because patient has high cognitive function • Nurse not familiar with packet

Table 3. Facilitators to implementation of cognitive stimulation and the corresponding Consolidated Framework for Implementation Research domains and constructs

Domain: Intervention Characteristics Construct: Design Quality • Designated section in electronic medical record Construct: Adaptability • Translate into other languages; have interpreter services at bedside • Consider using tablet or add more complex cognitive tasks to the packet for patients with higher cognitive function*
Domain: Outer Setting Construct: Patient Needs and Resources • Patient education on benefits of cognitive stimulation
Domain: Inner Setting Construct: Culture • Culture that supports research, quality improvement, and patient-centered care
Domain: Characteristics of Individuals Construct: Knowledge and Beliefs about the Intervention • Appreciation for importance of preventing delirium and benefits of cognitive stimulation
Domain: Process Construct: Engaging • Incorporating into work flow (add to daily task list and rounding report, administer with delirium assessment, checklist for cognition/delirium documentation; reminders (daily electronic reminders at 08:00 & 20:00)) • Education & training

*Reinforced by nurses by member checking

Table 4. Representative statements, extracted from field notes, by nurses regarding barriers to cognitive stimulation.

Barrier Theme	Field Note Extracts [Nurse ID]ŧ
Documentation - No designated section in electronic medical record	In Epic*, there's not a specific spot to document cog stim. You have to write it in as a comment. [001] There's no specific box in Epic*. [004]
Patient not cooperative/declines due to sedation, pain, agitation, fatigue, disinterest	Some patients are angry at the world and I'm trying to interact as little as possible with them, and this is an easy thing to just not do. [003] If I can barely get their meds in (because they are refusing things), I doubt I can get them to do the packet. [010] The hard part is with patients who are sedated but it's awesome for people who are awake and need a little push. [017]
Communication barriers (not English-speaking, visual or hearing impairment, restraints)	Patients who can't use their hands might not be able to do it. If they can talk, they can at least answer me when I ask them the questions, but if they can't use their hands or talk, they can't do it. For example, this happens with patients who are restrained. [002] Visual acuity can be a problem – if they can't see it. [009] We get a lot of Spanish speaking patients and we don't have translators who are present in person. [014]
Family does not support cognitive stimulation	The patient's family…they interfere with it, they give the patient the answer because they think they are helping or they don't want us do it. [019]
Cognitive stimulation not a priority	Nurses don't feel it's crucial. [013] If I'm busy……..It's lower in my priority list. [012] Somedays it's hard to get to it. You know, it's one more thing to add. [020]
Night shift not perceived as the appropriate time to do cognitive stimulation	I do it more during day shift than night. After 11P, I just want them to sleep. [010] We tuck them in, give meds, and treat symptoms. Night shift is a different culture. [021]
Nurse staff barriers (workload, staff turnover, lack of patient continuity)	I'm busy. We're understaffed. [002] I can't tell if it's helping, if the patients are benefitting. We don't have continuity so I don't know from one day to the next if it's helping. [002] I feel every couple of months there's an additional task added without consulting nurses. [011]

Burden of documentation	So much documentation that we have to go through, that little piece is sometimes missed. [008] We have to document so much, so sometimes it slips our minds. [016]
Packet Availability	People have written on them with permanent marker, and you have trouble finding a clean packet. [009]
Lack of understanding of, or appreciation for, evidence for cognitive stimulation	I think it's just to validate something. I think the CAM-ICU is good enough. We don't need to do more assessments. [022] I mean I see what the thought behind it is but our interaction is a better overall view. [018] For patients who are alert and oriented, it's useless. [002]
Nurse perceive that patient will be offended because patient has high cognitive function	For patients who are a RASS of 0, they look at us like why are they making us connect the dots? [009] They look at me like 'why am I doing this' because they are alert and oriented. [001]
Nurse not familiar with packet	I'm sorry, I'm a travel nurse. Can you tell me about it? [015] [Lack of] familiarity or comfort. [004]

*Epic is the electronic medical record.
ł Statements represents extracts from field notes and are not necessarily verbatim quotes
Abbreviations: CAM-ICU – Confusion Assessment Method for the ICU; RASS – Richmond-Agitation Sedation Scale.

Table 5. Representative statements, extracted from field notes, by nurses regarding facilitators for cognitive stimulation.

Facilitator Theme	Field Note Extracts [Nurse ID]ǂ
Designated section in electronic medical record	*If it had a separate section* [in Epic*]*, it would be easier.* [007] *Dropdown list with the options would be helpful.* [010]
Translate into other languages; Have interpreter services at bedside	*We use translators through phones. It's really hard for them to explain it over the phone….* [014]
Consider using tablet or add more complex cognitive tasks to the packet for patients with higher cognitive function**	*Maybe it would be more appealing if you could use a tablet instead of a paper packet.* [001]
Patient education on benefits of cognitive stimulation	*It's important to explain why you're doing it. I say 'we do this just to keep your brain active'.* [009]
Culture that supports research, quality improvement, patient-centered care	*I'm used to doing research so I don't mind doing anything to help patient care.* [005]
Appreciation for importance of preventing delirium and benefits of cognitive stimulation	*For some patients, it's really helpful, especially in long-term sedated patients. It helps them recover from delirium.* [014] *Good benefits…could help patients. Help understand cognitive outcomes.* [005] *I'm for it. Anything that prevents delirium.* [016]
Incorporating into work flow (add to daily task list, add to rounding report, administer with delirium assessment, checklist for cognition/delirium documentation; reminders (daily electronic reminders at 08:00 & 20:00))	*Maybe it would be helpful if the documentation for the following could be done all at the same time and in the same location in Epic (i.e. the same flowsheet): AM-PAC, HLM, CAM, cognitive stimulation.* [001] *The best time to do the packet is probably with the second assessment of the day. For the first assessment, you're just trying to catch up. After the first 4 hours, you've settled in.* [004] *We need a checklist to make sure all the nurses are being told where to document.* [005]
Education & training	*There has been a lot of education – I'm surprised to hear that nurses aren't documenting.* [005]

ǂ Statements represents extracts from field notes and are not necessarily verbatim quotes

Abbreviations: AM-PAC – activity measure for post-acute care; CAM-ICU – Confusion Assessment Method for the ICU; JH-HLM – [site de-identified] Highest Level of Mobility Scale; RASS – Richmond-Agitation Sedation Scale.

CHAPTER 5: OVERALL THESIS CONCLUSIONS

The overall goal of this thesis was to evaluate long-term complications of critical illness and evidence-based methods for reducing such complications as part of implementation in routine clinical practice.

In Chapter 2, I synthesized the existing literature on early rehabilitaton in the intensive care unit to improve physical functioning and mental health outcomes for survivors of critical illness. Building on this foundation of knowledge, in Chapter 3 (Section A), I conducted a systematic review and meta-analysis focused on an important mental health outcome, posttraumatic stress disorder (PTSD), among survivors of critical illness. This research demonstrated that approximately one in four survivors have clinically important PTSD symptoms at one year after critical illness. Risk factors for PTSD symptoms include benzodiazepine administration, mechanical ventilation, and post-ICU memories of frightening ICU experiences. PTSD symptoms are associated with worse quality of life. Based on existing published studies, there is limited evaluation of evidence-based interventions to address PTSD symptoms in this population. Further research is needed to address PTSD symptoms that commonly occur in survivors of critical illness.

In Chapter 3 (Section B), we further evaluated the most common mental health symptoms experienced by survivors of critical illness via analyses of a prospective longitudinal cohort study of 698 ARDS survivors from 41 hospitals in the U.S. This research demonstrated that psychiatric symptoms occurred in two-thirds of survivors over 12 months after critical illness. Younger age, female sex, unemployment, alcohol misuse, and greater opioid use in the intensive care unit were associated with greater psychiatric symptoms, while traditional markers of severity of illness were not, a finding that is consistent with my systematic review on PTSD symptoms (Chapter 3, Section A). Moreover, this research demonstrates that

survivors commonly have co-occurrence of symptoms of anxiety, depression and PTSD, suggesting that patient screening should consider each of these areas of mental health.

In Chapter 4 (Section A), we conducted a pre-post evaluation of prospectively collected data involving ARDS patients. This evaluation demonstrated that more patients in the post-quality improvement (QI) vs. pre-QI group received physical therapy in the ICU and were able to stand, transfer or ambulate during physical therapy in the ICU. Patients in the post- vs. pre-group had a significantly shorter time to first active physical therapy intervention in the ICU, and this shorter time to intervention was sustained over 5 years following the QI project. Patients in the post- vs. pre-group also had a greater proportion of ICU days with physical therapy after initiation. During both the pre- and post-QI period, severity of illness and sedation were independently associated with a longer time to initiation of active physical therapy intervention. This evaluation demonstrates sustained improvement in the delivery of evidence-based early rehabilitation via a structured quality improvement project.

In Chapter 4 Section B, the focus was on the early stage of implementation of evidence-based cognitive stimulation to reduce delirium in the ICU. This early stage investigation used qualitative methods to evaluate barriers and facilitators to implementation cognitive stimulation, as part of routine clinical practice in a medical ICU. Among 23 nurses providing semi-structured interviews, I identified 62 barriers to cognitive stimulation and 26 facilitators. The resulting themes (12 barrier and 9 facilitators) corresponded to the Consolidated Framework for Implementation Research (CFIR) domains: Intervention Characteristics, Outer Setting, Inner Setting, Characteristics of Individuals, and Process. Patient-specific variables (e.g. sedation) were the most frequently reported barriers to cognitive stimulation. Other barriers included: cognitive stimulation not a priority; staffing barriers; documentation burden; and lack of appreciation for evidence supporting cognitive stimulation.

In conclusion, survivors of critical illness experience clinically important impairments in physical, cognitive and mental health that can last for years after discharge from the ICU and are associated with worse quality of life. Evidence-based interventions for prevention and treatment include early physical and cognitive interventions in the ICU. The use of structured quality improvement processes, including understanding potential barriers and facilitators to implementation, can play an important role to sustain implementation of such interventions.

APPENDIX

Chapter 3 – Section A Tables

Table 1: Study cohort characteristics, ordered by follow-up time

Study 1st author	Study type	N	Inclusion (I) and exclusion (E) criteria	Male (%)	Mean (S.D.) or *median (interquartile range)* [absolute range]					
					Age in years	Days in hospital	Days in ICU	Days of MV	APACHE II score	Follow-up in months
Treggiari et al.[19]	Randomized controlled trial	65[a] 64[b] 129	I: Age>16 yrs, medical & surgical ICU, required intubation & expected to receive MV ≥12 hrs E: Neurologic conditions with expected best d/c GCS≤8, neuromuscular disease requiring ventilatory support, creatinine >2.0 mg/dL or requiring renal replacement therapy, allergy to benzodiazepines or morphine, epilepsy, drug overdose, liver failure class Child-Pugh C, pregnancy, mental disability or inability to cooperate, receipt of HIV protease inhibitors or erythromycin	75[a] 78[b]	63[a] (15) 60[b] (16)	*16*[a] [12-32] *20*[b] [13-38]	*4*[a] [1-129] *5*[b] [2-99]	3[a] (5) 5[b] (11)	60[a,c] (28) 60[b,c] (27)	0,1
Rattray et al.[34,51]	Prospective cohort	109	I: Age≥18 yrs, general ICU LOS ≥24hrs E: Died prior to hospital d/c, unable to give consent, lost to follow up, refused consent, stayed in hospital for >6 m, Living >100 miles away	61	54 [18-80]	*28* [5-165]	*5* [1-57]	-	18 [5-33]	0, 6, 12
Twigg et al.[33]	Case series cohort	44	I: Age≥18 yrs, ICU LOS ≥48 hrs E: English difficulties, dementia or learning disabilities, self-inflicted injury/overdose (psychological comorbidity), unable to consent in 4–14 d after ICU d/c due to confusion, d/c before approach	45	*5*[d] [18-74]	-	*1*[d] [2-32]	*8*[d] [1-20]	*16*[d] [3-35]	0.13-0.5, 2, 3

Wallen et al.[35]	Prospective cohort	100	I: Age>18 yrs; medical, surgical & trauma ICU; ICU LOS ≥24 hrs; could speak, read, & write English E: Transferred from the ICU because of expected death, d/c to home or another health care facility, confused state, anxiety disorder	68	*63* [18-89]	*2* [1-31]	*2* [1-31]	-	*13* [2-40]	1
Jones et al.[13]	Randomized controlled trial	177[a] 175[b] 352	I: MV ≥24 hrs, ICU LOS ≥72 hrs E: Too confused to give informed consent, pre-existing psychotic illness or PTSD	69[a] 59[b]	*60*[a] [18-81] *59*[b] [18-82]	-	*13*[a] [3-79] *13*[b] [3-71]	*9*[a] [1-62] *10*[b] [1-50]	*20*[a] [5-46] *18*[b] [2-39]	1, 3
Myhren et al.[36-38]	Prospective cohort	255	I: Age 18-75 yrs; general, medical & CCU; ICU LOS ≥24 hrs E: Language difficulties, serious psychiatric problems, severe head injury, cognitive failure	63	48 (16)	-	12	11	SAPS II: 37	1-1.5, 3, 12
Perrins et al.[39]	Prospective cohort	72	I: Age>18 yrs, general ICU LOS ≥ 24 hrs E: History of mental illness, history of head trauma, lack of consent, active bereavement, non-English speaking	-	49 (16)	32 (19)	6 (5)	-	-	1.5, 6, 12
Samuelson et al.[40]	Prospective cohort	250	I: Age>18 yrs, MV, general ICU LOS ≥24 hrs E: Head injury, psychotic illness, mental retardation, intoxication, admitted following suicide attempt, hearing/speech disability, non-Swedish speaking, transferred to another hospital, MV at d/c, MV >24 hrs preadmission	52	63 (13)	-	6 (6), *4*	4 (5), *2*	*18*	2
Jones et al.[22]	Randomized controlled trial	69[a] 57[b] 126	I: MV, mixed general ICU LOS ≥48 hrs E: Burn injury, neurosurgical patient, preexisting psychotic illness, speech/reading difficulty, life expectancy <6 m	54[a] 58[b]	57[a] (17) 59[b] (16)	-	14[a] (20) 13[b] (18)	-	17[a] (5) 16[b] (5)	2, 6

Study 1st author	Study type	N	Inclusion (I) and exclusion (E) criteria	Male (%)	Mean (S.D.) or *median (interquartile range)* [absolute range]					
					Age in years	Days in hospital	Days in ICU	Days of MV	APACHE II score	Follow-up in months
Weinert et al.[41]	Prospective cohort	277	I: Adult patients, MV for >36 hrs, medical & surgical ICU E: Craniotomy, coma, life support withdrawal, pre-ICU psychosis, on ventilator at other hospital >3 d, difficult communication, cognitive impairment, can't be reached	52	*55 (47-65)*	-	-	*7 (4-17)*	-	2, 6
Jones et al.[42]	Prospective cohort	304	I: Age>18 yrs , MV, mixed general ICU LOS ≥ 48 hrs E: Prior PTSD, admitted following suicide attempt, preexisting or concomitant psychotic illness, resides >30 km from hospital, unresolved confusion, enrolled in another research study	62	*61* [17-86]	-	*7* [2-76]	*3* [2-90]	*16* [3-36]	3
Cuthbertson et al.[43]	Prospective cohort	111	I: In general ICU E: -	56	*58* [18-87]	-	*6* [1-51]	*2* [0-44]	*18* [4-38]	3
Griffiths et al.[44]	Prospective cohort	127	I: General medical ICU LOS ≥3 d, Age>18 yrs E: Unable to read/understand English	66	57 [17-85]	-	*12* [2-101]	-	-	3
Costa et al.[45]	Prospective cohort	138	I: Age > 18 yrs, ICU LOS ≥24 hrs, stayed on MV E: Known pre-existing mental or terminal illness; admission for attempted suicide; inability to speak; neurologic deficit after ICU d/c; did not return for outpatient clinic	69	43 (17)	-	10 (8)	7	-	3

Schandl et al.[46]	Prospective cohort	61	I: Patients d/c from surgical, medical & general ICU, ICU LOS ≥4 d or patients with shorter ICU stay due to severe confusion or hallucination in ICU E: -	64	53 (18)	-	*7* [4-37]	-	21 (9)	3, 6, 12
Sukantarat et al.[47]	Prospective cohort	51	I: General ICU LOS ≥ 72 hrs E: Major medical or surgical therapy following d/c, reluctance to undergo detailed testing, still in hospital at time of study, lived at a distance	43	57 (14)	-	17 (17)	12 (17)	15 (6)	3, 9
Jackson et al.[21]	Randomized controlled trial	89[a] 91[b] 180	I: Age>18 yrs, medical ICU, required MV for >12 hrs E: Post-cardiopulmonary arrest, continuous MV >2 wks, moribund state and/or life support withdrawal, profound neurological deficits that prevented independent living, enrollment in another trial, underwent cardiac surgery or neurosurgery, or stroke before or during the trial	54[a] 45[b]	*65*[a] *(53-73)* *68*[b] *(56-76)*	-	-	-	*28*[a] *(22-34)* *28*[b] *(21-33)*	3, 12
Granja et al.[48]	Prospective cohort	313	I: Age≥18 yrs, ICU LOS >48 hrs E: -	58	*59 (44-71)*	-	*8 (5-13)*	-	SAPS II: *37 (30-46)*	6
Cuthbertson et al. (PRaCTICal study)[20]	Randomized controlled trial	143[a] 143[b] 286	I: Age≥18 yrs, ICU care during hospital stay, surviving until hospital d/c E: Not expected to survive to leave hospital, unable to complete questionnaires or attend clinics, did not consent to participate	60[a] 60[b]	*59*[a] *(46-49)* *60*[b] *(46-71)*	-	*3*[a] *(2-10)* *3*[b] *(1-7)*	-	*19*[a] *(15-24)* *19*[b] *(15-24)*	6, 12
Van Der Schaaf et al.[23]	Cross-sectional	255	I: Mixed adult ICU, ICU LOS > 48 hrs E: -	66	59 (17)	-	9 (10)	6 (8)	14 (6)	12
Garrouste-Orgeas et al.[14]	Prospective single-center longitudinal study	49[a] 94[b] 143	I: Medical-surgical ICU, ICU LOS ≥4d E: Died on ICU day 4, not fluent in French, dementia, unwillingness of family to participate, no visits from relatives on d/c day	67[a] 53[b]	65[a] (17) 65[b] (15)	-	18[a] (23) 17[b] (17)	-	41[a] (15) 42[b] (14)	12

Study 1st author	Study type	N	Inclusion (I) and exclusion (E) criteria	Male (%)	Mean (S.D.) or *median (interquartile range)* [absolute range]					
					Age in years	Days in hospital	Days in ICU	Days of MV	APACHE II score	Follow-up in months
Badia-Castelló et al.[49]	Prospective cohort	169	I: Age > 16 yrs, ICU LOS > 24 hrs, E: Being transferred to other centers, coronary artery disease, traumatic brain injury, foreigners, known pre-existing neurologic or psychiatric disease	69	54 (18)	*21 (13-35)*	*6 (3-13)*	-	-	12
Scragg et al.[24]	Cross-sectional	142	I: General ICU survivors E: Head trauma, accidental or non-accidental injury, admitted for routine surgery without complications	53	*57* [19-90]	-	[1-33]	-	-	13 (6) [3–21]
Schandl et al.[32]	Quasi-experi-mental	156[a] 102[b] 258	I: Age≥16 yrs, ICU LOS ≥ 96 hrs. E: Not fluent in Swedish, no address	65[a] 63[b]	53[a] (17) 53[b] (18)	-	11[a] (7) 9[b] (7)	-	22[a] (9) 20[b] (9)	14
Richter et al.[50]	Prospective cohort	37	I: Surgical ICU, ICU LOS ≥ 30 d E:-	76	42 (17)	-	52 (20)	-	20 (7)	35 (14)
Bugedo et al.[31]	Prospective cohort	132[a] 155[b]	I: Age >18 yrs; anticipated MV >48 hrs E: pre-existing neurologic disease; pre-existing end-stage liver & renal failure; second period of MV during hospitalization; MV >24 hours before ICU transfer; drug abuse; high expected short term mortality	50[a] 57[b]	59 (19)[a] 60 (18)[b]	18 (10-31)[a] 18 (10-33)[b]	11 (6-18)[a] 10 (6-15)[b]	7 (4-16)[a] 8 (4-13)[b]	17 (12-22)[a] 18 (15-22)[b]	12
Paparrigopoulos et al[26]	Cross-sectional	48	I: Adult patients, ICU LOS > 24 hrs E:-	69	52.7 (2.8)	36 (8)[e]	13.2 (2.6)	-	11.8 (4.8)	21 (3)

Study 1st author	Study type	N	Inclusion (I) and exclusion (E) criteria	Male (%)	Mean (S.D.) or *median (interquartile range)* [absolute range]					
					Age in years	Days in hospital	Days in ICU	Days of MV	APACHE II score	Follow-up in months
Davydow et al[29,30]	Prospective cohort	120	I: Medical & Surgical ICU; ICU LOS >24 hrs E: Admission diagnosis of traumatic injury or suicide attempt; pre-existing cognitive impairment or dementia; communication/language barrier; pre-existing medical illness with life expectancy <12 months	57.5	49 (14.6)	16.7 (12.1)	7.5 (8.2)	2.5 (6.9)	25.9 (15.3)	3,12
Azoulay et al.[28]	Prospective cohort	574[f] 134[g]	I: Adult ICU patients with acute respiratory failure requiring NIV E: -	63.6[f] 53.7[g]	*66 (57-76)[f]* *76 (65-83)[g]*	*16 (8-30)[f]* *15 (7-2)[g]*	*6 (3-12)[f]* *6 (3-15)[g]*	-	*36 (27-47)[f]* *41 (35-51)[g]*	0,3
Wade et al.[27]	Prospective cohort	100	I: General adult ICU patients requiring MV >24hrs or ≥2 organs supported E: non-English speaking; pre-existing dementia; remained confused or had low Glasgow Coma Scale until ICU discharge; had severe sensory impairment; terminally ill	52	57.3 (17.4)	27 (239)	8 (85)	3 (80)	22. (7)	3
Van Ness et al.[52]	Prospective cohort	152	I: Included in the Evaluation of Psychoactive Medications in the Intensive Care Unit (EPIC) study E: No proxy available for information; death before the proxy interview; transferred from another ICU; admission <24 hours; non–English speaking.	41%	66-75	-	-	-	-	-

Strom et al.[18]	Randomized controlled trial	13[a] 13[b] 26	I: Age ≥18 yrs; medical & surgical ICU; required intubation & MV >24 hrs E: Pregnancy; increased intracranial pressure; sedation indicated for medical diagnosis (e.g., seizures or therapeutic hypothermia)	31%[a] 38%[b]	*71*[a] (*54-74*) *63*[b] (*56-67*)	-	-	-	*20*[a] *(16-29)* *25*[b] *(21-26)*	*21*[a] (*17-25)* *23*[b] *(18-26)*
Sackey et al.[17]	Randomized controlled trial	20[h] 20[i] 40	I: Age ≥18 yrs; general ICU; MV & sedation >12 hrs E: Intracranial pathology; family history of malignant hyperthermia; dialysis at inclusion; pregnancy; continuous sedation >18 hrs before inclusion	50%	58[h] (39-80) 57[i] (19-80)	-	160 (183)[h] 188 (181)[i]	-	19[h] (5-37) 18[i] (4-32)	6
Nickel et al.[25]	Cross-sectional	41	I: Age 18-65 yrs; treatment duration ≥ 24 h E: -	68%	47	12 (5)	-	-	12 (11)	6 [3-15]
Jones et al.[53]	Case series cohort	45	I: ICU stay >24hrs, required MV E: Admission diagnosis of suicide attempt or head injury; prior or current psychotic illness	44%	*57* [17-82]		*8* [1-60]		*17* [4-28]	0.5, 2
Girard et al.[54]	Prospective cohort	43	I: Medical & coronary care ICUs; MV E: Neurological disease impairing cognitive function or mental retardation; communication barrier because non-English speaking or sensory deficits	47%	*52 (39-65)*		*10 (5-13)*	*5 (3-12)*	*25 (20-31)*	6

APACHE II indicates acute physiology and chronic health evaluation II score; CCU, coronary care unit; CPR, cardiopulmonary resuscitation; d, days; d/c, discharge; HIV, human immunodeficiency virus; hrs, hours; ICU, intensive care unit; LOS, length-of-stay; m, months; MV, mechanical ventilation; NIV, non-invasive ventilation; PTSD, posttraumatic stress disorder; SAPS simplified acute physiology score; wks, weeks; yrs, years; -, not reported.

a = Intervention group
b = Control group
c = APACHE III score
d = Values of patients in one of two hospitals, from which most patients were recruited.
e = hospital length of stay in addition to ICU length of stay
f = No treatment limitations
g = Do not intubate
h = randomized to receive isoflurane
i = randomized to receive midazolam

Table 2: Measurements of PTSD symptoms/PTSD diagnosis, ordered by follow-up time

Study	Past psychiatric illness	Instrument	Follow-up in months	N at follow-up	Mean (S.D.) or *median (IQR)* [range]	Cut-off score	Point prevalence
Treggiari et al.[19]	-	PCL, IES-R	0 1	109 102	- -	- *DSM-IV* criteria	- 9%[a], 10%[b]
Twigg et al.[33]	-	PDS IES	3 3	44 44	- -	*DSM-IV* criteria IES > 19	16% 23%
Rattray et al.[34,51]	-	IES-I IES-A	0.75 6 12 0.75 6 12	109 61 80 109 61 80	7 (3) 6 (3) 7 (3) 6 (3) 4 (5) 6 (4)	 20 20	 18%[c] 20%[c]
Wallen et al.[35]	-	IES-R	1	100	18 (13)	≥33	13%
Jones et al.[13]	29%	PTSS-14	1 3	352 322	*22* [14-84][a], *25* [13-65][b] *24* [12-36][a], *24* [12-36][b]	≥45 ≥45	- 5%[a], 13%[b]
Myhren et al.[38]	-	IES	1-1.5	255	23	≥35	27%
Myhren et al.[37]	-	IES	1-1.5 3 12	255 192 180	- - 22	- - ≥20 ≥35	- - 50% 27%
Perrins et al.[39]	-	IES	1.5 6 12	44 41 38	14 12 12	19	31% 32% 27%
Samuelson et al.[40]	-	IES-R	2	226	8 (12)	30	8%
Jones et al.[22]	-	IES	2 6	63[a], 51[b], 114 58[a], 44[b], 102	20[a], *14* 23[a], *20*	- 19	- 53%[a], 48%[b], 51%

Weinert et al.[41]	-	PDS PTSD-like severity score	2 6 2 6	149 80 149 80	- - - -	*DSM-IV* criteria ≥11	17% 15% 21% 23%
Jones et al.[42]	24%	PDS	3	238	-	*DSM-IV* criteria	9%
Cuthbertson et al.[43]	14%	DTS	3	78	*8* [0-87]	27	22%
Griffiths et al.[44]	-	TSQ	3	108	-	6	52%
Costa et al.[45]	-	IES-I IES-A IES-H	3 3 3	90 82 88	4 (3) 5 (5) 4 (3)	> 20 & ≥33	14% & 5%
Schandl et al.[46]	-	IES	3 6 12	30 30 30	23 (16) 19 (14) 19 (16)	>25	46% (n = 61)[i] - -
Sukantarat et al.[47]	-	IES	3 9	51 45	- -	26	35% 62%
Jackson et al.[21]	-	PTSS-10	3 12	80 63	*22 (12-29)*[a], *20 (14-26)*[b] *23 (16-31)*[a], *22 (15-34)*[b]	>35 >35	14%[a], 10%[b] 24%[a], 24%[b]
Granja et al.[48]	-	PTSS-14	6	299	-	≥49	18%
Cuthbertson et al. (PRaCTICal study)[20]	-	DTS-I DTS-S DTS-I DTS-S	6 6 12 12	213 212 189 187	16 (16)[a], 19 (17)[b] 12 (14)[a], 15 (16)[b] 14 (14)[a], 17 (15)[b] 10 (14)[a], 12 (13)[b]	-	-
Van Der Schaaf et al.[23]	-	IES	12	238	*10 (1-29)* [0-75]	>35	18%

Study	Past psychiatric illness	Instrument	Follow-up in months	N at follow-up	Mean (S.D.) or *median (IQR)* [range]	Cut-off score	Point prevalence
Garrouste-Orgeas et al.[14]	22%	IES-R	12	56	21 (12)[a], 32 (15)[b]	≥22	62%
Badia-Castelló et al.[49]	-	IES	12	38[d] 90[d] 41[d]	1 (6)[d] 6 (8)[d] 11 (12)[d]	-	-
Scragg et al.[24]	-	IES	13[e]	77	-	30	16%
Schandl et al.[32]	16%	IES	14	171	*18*[a]*, 19*[b]	-	-
Richter et al.[50]	49%	Semi structured psychiatric interview	35[f]	37	-	*DSM-IV* criteria	32%[g], 19%[h], 13%[h]
Bugedo et al.[31]	-	PTSS-10 scale	12	35[a] 40[b]	*26 (17-38)*[a] *28 (19-30)*[b]	>35 >35	26% 28%
Paparrigopoulos et al.[26]	42%	DTS	21 (3)	48	24 (4)	40	25%
Davydow et al.[29]	32.3% (depression only)	PCL-C	3 12	80 76	- -	*DSM-IV* criteria	17% 14%
Davydow et al.[30]	26.9%	PCL-C	3 12	131 120	- -	*DSM-IV* criteria	16% (10%-23%) 15% (9%-21%)
Azoulay et al.[28]	-	IES-R	3	120[j] 34[k]	*3 (0-10)*[j] *2 (0-8)*[k]	-	-
Wade et al.[27]	16%	PDS	3	100	-	18	27%
Van Ness et al.[52]	-	PTSS-10	1	152	-	≥35	8%

Study	Past psychiatric illness	Instrument	Follow-up in months	N at follow-up	Mean (S.D.) or *median (IQR)* [range]	Cut-off score	Point prevalence
Strom et al.[18]	8%[a] 23%[b]	IES-R PTSS-10	*21 (17-25)*[a] *23 (18-26)*[b]	13[a] 13[b] 13[a] 13[b]	*4(2-8)*[a] *2(0-11)*[b] *3 (0-6.5)*[a] *10 (6-17)*[b]	>32 >35	8%[a] 15%[b] 8%[a] 0%[b]
Sackey et al.[17]	-	IES	6	10[a] 7[b]	*26.6(23.7)*[a] *22.8(29.7)*[b]	> 25	60% 33%
Nickel et al.[25]	41.5%	PTSS-10 SCID	6 [3-15]	41 4	-	>35 *DSM-IV* criteria	17.1% 9.8%
Jones et al.[53]	15.6%	IES	2	45	-	-	-
Girard et al.[54]	-	PTSS-10	6	43	*21 (14-30)*	>35	14%

DSM-IV indicates Diagnostic and Statistical Manual of Mental Disorders – 4th Edition; DTS-I, Davidson Trauma Scale-Incidence subscale; DTS-S indicates Davidson Trauma Scale-Severity subscale; IES-A indicates Impact of Events Scale–Avoidance Subscale; IES-I, Impact of Events Scale–Intrusion Subscale; IES-H, Impact of Events Scale–Hyperarousal Subscale; IES-R, Impact of Events Scale-Revised; n/a, not applicable; PCL, Posttraumatic stress disorder Checklist; PCL-C, Posttraumatic stress disorder Checklist – Civilian Version; PDS, Posttraumatic Diagnostic Scale; PTSD, posttraumatic stress disorder; PTSS-10, Posttraumatic Symptom Scale-10; PTSS-14, Post Traumatic Symptom Scale-14; SCID, Structured Clinical Interview for DSM-IV; TSQ, Trauma Stress
Questionnaire; -, not reported.

a = Intervention group
b = Control group

c = Clinically significant symptoms of intrusion (I) or avoidance (A)
d = Values of three groups namely no memory, without illusion memories and with illusion memories groups respectively
e = Cross-sectional study with mean (SD) follow up of 13 (6) months and range of 13-21 months
f = Prospective study with mean (SD) follow up of 35 (14) months
g = Prevalence including both full PTSD-diagnosed patients and sub-syndromal PTSD-diagnosed patients
h = Prevalence of full PTSD-diagnosed patients and sub-syndromal PTSD-diagnosed patients respectively
i = Prevalence based on total of 61 patients completing the PTSD symptom assessment over the 12 month follow-up period
j = no treatment limitation decisions
k = code status is “do not intubate”

Table 3. Risk of bias assessment for randomized controlled trials.

Study	Adequate sequence generation?	Allocation concealment?	Blinding of participants, staff, and outcomes assesors?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Cuthbertson et al.[20]	+	-	-	+	+	+
Jones et al.[22]	+	+	+	-	?	+
Jackson et al.[21]	+	+	-	+	+	+
Treggiari et al.[19]	+	+	-	+	?	+
Jones et al.[13]	+	-	-	+	?	+
Strom et al.[18]	+	+	-	-	+	+
Sackey et al.[17]	?	?	-	-	?	?

Based on Cochrane criteria for assessing risk of bias in randomized controlled trials. "+" means Cochrane criteria met (i.e., low risk of bias). "-" means Cochrane criteria not met (i.e., high risk of bias). "?" means unclear if Cochrane criteria met (i.e., unclear risk of bias).

Table 4. Risk of bias assessment for observational studies, based on the Newcastle Ottawa Scale

Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure (s)	Demonstration that outcome was not present at start	Comparability of cohorts	Assessment of outcome	Was follow-up long enough for outcome to occur?	Adequacy of follow-up
Rattray[34]	*	*	*	*	+	*	*	*
Perrins[39]			*	*	+	*	*	
Samuelson[40]	*	*	*	*	++	*	*	*
Jones[42]	*	*	*	*	+	*	*	*
Cuthbertson[43]	*	*	*	*	+	*	*	*
Griffiths[44]	*	*	*	*	+	*	*	*
Sukantarat[47]	*	*	*	*	+	*	*	
Rattray[51]	*	*	*	*	+	*	*	*
Twigg[33]	*	*	*	*	+	*	*	
Wallen[35]	*	*	*	*	++	*	*	*
Myhren[38]	*	*	*	*	++	*	*	?
Myhren[37]	*	*	*	*	++	*	*	*
Myhren[36]	*	*	*	*	++	*	*	*
Weinert[41]	*	*	*	*	+	*	*	*
Schandl[46]	*	*	*	*	+	*	*	*
Granja[48]	*	*	*	*	++	*	*	*
Garrouste-Orgeas[14]	*	*	*	*	+	*	*	
Schandl[32]	*	*	*	*	++	*	*	*
Richter[50]	*	*	*	*	+	*	*	*
Bugedo[31]	*	*	*	*	+	*	*	
Davydow[29]	*	*	*	*	++	*	*	*
Davydow[30]	*	*	*	*	++	*	*	*
Azoulay[28]	*	*	*	*	+	*	*	
Wade[27]	*	*	*	*	++	*	*	*
Van Ness[52]	*	*	*	*	++	*	*	
Jones[53]	*	N/A	*	?	N/A	*	*	N/A
Van der Schaaf[23†]	*	*	*	*	++	*	*	N/A
Da costa[45]	*	*	*	*	+	*	*	
Badia-Castello[49]	*	*	*	*	++	*	*	
Girard[54]	*	*	*	*	++	*	*	*
Nickel[25†]	*	*	*	*	+	*	*	N/A
Scragg[24†]	*	*	*	*	++	*	*	N/A
Paparrigopoulos[26†]	*	*	*	*	++	*	*	N/A

Legend: * = low risk of bias; ? = unclear risk of bias; blank = high risk of bias; + study controlled for type of ICU; ++ = study controlled for additional covariates; N/A = not applicable

[†]Cross-sectional studies

Table 5: Potential risk factors for PTSD

Study (n)	Measure of association	Potential risk/protective factor	Outcome: post-traumatic stress symptoms/disorder
Treggiari et al. (*n* = 109)[19]	Two-sample *T* test χ^2 test	Light vs. deep sedation	Normalized PTSD score, mean ranks: 46 (29)[a] vs. 56 (29)[b], *p* = 0.07 Presumptive PTSD diagnosis: 9%[a] vs. 10%[b], *p* = 0.83
Rattray et al. (*n* = 106)[51]	Correlational analyses (using square root transformation)	(a) Awareness of surroundings (b) Frightening experiences (c) Recall of ICU experiences (d) Satisfaction with ICU care	(a) *rho* = -0.046 (IES-A) and -0.038 (IES-I) at d/c, n.s. *rho* = -0.043 (IES-A) and 0.007 (IES-I) at 6 m, n.s. *rho* = -0.095 (IES-A) and -0.030 (IES-I) at 12 m, n.s. (b) *rho* = 0.515 (IES-A) and 0.600 (IES-I), *p* < 0.01 for both at d/c *rho* = 0.458 (IES-A) and 0.437 (IES-I), *p* < 0.01 for both at 6 m *rho*=0.470 (IES-A) and 0.413 (IES-I), *p* < 0.01 for both at 12 m (c) *rho* =-0.354 (IES-A), *p*<0.01 and -0.263 (IES-I), *p*< 0.05 at d/c *rho*=-0.275 (IES-A) and -0.302 (IES-I), *p* < 0.05 for both at 6 m *rho* = -0.193 (IES-A) and -0.121 (IES-I) at 12 m, n.s. (d) *rho* = -0.134 (IES-A) and -0.080 (IES-I) at d/c, n.s. *rho* = -0.035 (IES-A) and -0.026 (IES-I) at 6 m, n.s. *rho* = -0.127 (IES-A) and -0.039 (IES-I) at 12 m, n.s.
Rattray et al. (*n* = 60-80)[34]	Repeated measures ANOVA Pearson's correlation	(a) Time since hospital d/c (d/c, 6 m, 12 m) (b) Sex (c) Age (d) APACHE II score (e) ICU LOS (f) Hospital LOS (g) Awareness of surroundings in ICU (hospital d/c) (h) Frightening ICU memories (hospital d/c)	<u>IES scores (square root)</u> (a) 2.4 vs. 2.1 vs. 2.4 (IES-A), *p* = 0.34 2.7 vs. 2.4 vs. 2.6 (IES-I), *p* = 0.42 (b) n.s. (c) *rho* = −0.25 with IES-A at hospital d/c, *p* = 0.02 *rho* = −0.38 with IES-A at 6 m, *p* = 0.003 *rho* = −0.33 with IES-A at 12 m, *p* = 0.003 *rho* = −0.41 with IES-I at hospital d/c, *p* = 0.0002 *rho* = −0.27 with IES-I at 6 m, *p* = 0.04 *rho* = −0.32 with IES-I at 12 m, *p* = 0.004 (d) n.s. (e) *rho* = 0.26 with IES-I at 12 m, *p* = 0.02 (f) *rho* = −0.25 with IES-I at hospital d/c, *p* = 0.02 (g) n.s. (h) *rho* = 0.43 with IES-A at hospital d/c, *p* < 0.0001 *rho* = 0.43 with IES-A at 6 m, *p* = 0.0006

Study (n)	Measure of association	Potential risk/protective factor	Outcome: post-traumatic stress symptoms/disorder
	Multivariable regression analysis	(i) Satisfaction with ICU care (hospital d/c) (j) Recall of ICU experience (hospital d/c) (k) IES-A at hospital d/c (l) IES-I at hospital d/c	*rho* = 0.47 with IES-A at 12 m, $p < 0.0001$ *rho* = 0.53 with IES-I at hospital d/c, $p < 0.0001$ *rho* = 0.39 with IES-I at 6 m, $p = 0.002$ *rho* = 0.41 with IES-I at 12 m, $p = 0.0002$ (i) n.s. (j) *rho* = -0.29 with IES-I at hospital d/c, $p = 0.009$ (k) $\beta_{st} = 0.42$ with IES-A at 6 m, $p = 0.001$; $\beta_{st} = 0.19$ with IES-A at 12 m, $p = 0.10$ (l) $\beta_{st} = 0.46$ with IES-I at 6 m, $p = 0.001$; $\beta_{st} = 0.50$ with IES-I at 12 m, $p \leq 0.0005$
Wallen et al. (*n* = 100)[35]	Univariate and multivariate logistic regression analysis	(a) Age<65 yrs (b) Sex (male) (c) APACHE II score (d) ICU LOS (e) Emergency admission (f) Hospital LOS	(a) Multivariate: OR 5.63 (1.17-26.89), $p = 0.03$ <u>Univariate</u> (b) OR 1.39 (0.42-4.64), $p = 0.59$ (c) OR 0.87 (0.77 to 0.98), $p = 0.02$ (d) OR 0.99 (0.98-1.01), $p = 0.20$ (e) OR 0.94 (0.24-3.75), $p = 0.93$ (f) OR 0.79 (0.54-1.14), $p = 0.20$
Jones et al. (*n* = 352)[13]	Fisher's exact test Mann-Whitney *U* χ^2 test Nonparametric tests	(a) Gender (b) Recalling delusional memories (c) ICU diary	(a) $p = 0.92$, n.s. (b) $p = 0.013$ (c) Median PTSS-14: *24*[a] *vs. 24*[b], n.s. at 3 m New-onset PTSD: 5%[a] vs. 13%[b], $p = 0.02$ at 3 m Median change in PTSS-14 (for group with a baseline score ≥45): *-23*[a] *vs. -2*[b], $p = 0.04$
Myhren et al. (*n* = 255)[38]	Multivariable linear regression analysis	(a) Age (b) Employment status (c) Respirator treatment (d) Life orientation test (e) Pain memories (f) Lack of control (g) Unable to express needs (h) Gender	(a) $\beta = 0.17$, $p = 0.007$ (b) $\beta = 9.02$, $p < 0.001$ (c) $\beta = 7.07$, $p = 0.004$ (d) $\beta = -0.87$, $p < 0.001$ (e) $\beta = 2.19$, $p = 0.004$ (f) $\beta = 3.18$, $p < 0.001$ (g) $\beta = 2.00$, $p = 0.012$ (h) $\beta = 2.30$, $p = 0.244$

Study (n)	Measure of association	Potential risk/protective factor	Outcome: post-traumatic stress symptoms/disorder
Myhren et al. (*n* = 255)[37]	Multivariable logistic regression analysis	(a) Type of disease (b) Education (c) Personality trait (pessimism) (d) Pain memories (e) Factual memories <u>Risk factors for delayed PTSD</u> (a) Unemployment (b) ICU LOS (c) MV (d) Personality trait (optimism)	(a) n.s. (b) OR 0.38 (0.15 to 0.95), *p* = 0.038 (c) OR 0.91 (0.84 to 0.99), *p* = 0.029 (d) OR 1.46 (1.05 to 2.04), *p* = 0.025 (e) OR 6.61 (1.41 to 31.0), *p* = 0.017 (a) OR 3.1 (1.1 to 8.7), *p* = 0.035 (b) OR 1.1 (1.0 to 1.1), *p* = 0.005 (c) OR 0.3 (0.1 to 0.8), *p* = 0.014 (d) OR 1.1 (1.0 to 1.3), *p* = 0.028
Perrins et al. (*n* = 44)[39]	Mann-Whitney *U* Kruskal-Wallis one-way ANOVA	(a) Sex (b) Trauma (c) Respiratory failure (d) No recall of the ICU (e) Lack of social support (f) Admitted to ICU via ED (g) Admitted conscious from a ward to ICU	(a) n.s. (b) High IES and IES-A scores at 6 weeks, *p* < 0.05 (c) High IES score at 6 weeks, *p* < 0.05 (d) n.s. (e) n.s. (f) High IES score at 6 weeks, *p* < 0.05 (g) High IES-A scores at 6 weeks, *p* < 0.02
Samuelson et al. (*n* = 226)[40]	Mann-Whitney *U* or χ2 or Fisher's exact test	(a) Younger age (b) Female sex (c) APACHE II (d) ICU LOS (e) Days of MV (f) Propofol in ICU (g) Midazolam in ICU (h) Ketobemidone in ICU (i) Neuromuscular blocker in ICU Proportion of total ICU stay with MAAS score… (j) …0–2 (k) …3 (l) …4-6 (m) Complete amnesia of ICU 5 d post-ICU	**<u>Comparisons: PTSD vs. no PTSD</u>** (a) *Mean 57 vs. 64 yrs, p = 0.04* (b) *74% vs. 46%, p = 0.04* (c) *Median 13 vs. 18, p = 0.09* (d) *Median 2.7 vs. 3.6, p = 0.42* (e) *Median 1.8 vs. 1.6, p = 0.97* (f) *95% vs. 93%, p = 1.00* (g) *68% vs. 30%, p = 0.02* (h) *79% vs. 82%, p = 0.76* (i) *5% vs. 13%, p = 0.71* (j) *Median 22% vs. 27%, p = 0.66* (k) *Median 62% vs. 67%, p = 0.48* (l) *Median 11% vs. 0%, p = 0.06* (m) *16% vs. 19%, p = 1.00*

Study (n)	Measure of association	Potential risk/protective factor	Outcome: post-traumatic stress symptoms/disorder
	Multivariable logistic regression - Model 1 Multivariable logistic regression - Model 2	(n) "Delusional memories" of ICU 5 d post-ICU (o) "Delusional memories" of ICU without factual recall 5 d post-ICU (p) No. of recalled extremely stressful events 5 d post-ICU (q) Recall of feeling fearful in ICU 5 d post ICU (r) Nightmares 5 d post-ICU (s) HAD anxiety score 5 d post-ICU (t) HAD depression score 5 d post-ICU (u) Female sex (v) MAAS score 4-6 (w) Recall of greater number of extremely stressful events 5 d post-ICU (x) Female sex (y) MAAS score 4–6 (z) Recall of feeling fearful in ICU 5 d post ICU	(n) *42% vs. 33%, p = 0.57* (o) *0% vs. 3%, p = 1.00* (p) *Median 3 vs. 1, p = 0.03* (q) *37% vs. 8%, p = 0.001* (r) *16% vs. 13%, p = 0.72* (s) *Median 5 vs. 2, p = 0.006* (t) *Median 7 vs. 4, p = 0.001* (u) *OR = 4.7, p = 0.005* (v) *OR = 1.74 per 0.1 higher MAAS, p = 0.005* (w) *OR = 1.1, p = 0.008* (x) *OR = 4.9, p = 0.004* (y) *OR = 1.77 per 0.1 higher MAAS, p = 0.005* (z) *OR = 7.0, p = 0.002*
Jones et al. (*n* = 102)[22]	One-way ANOVA Fisher's exact test	(a) No self-help rehabilitation manual (b) "Delusional memories" of ICU 2 w after ICU d/c	(a) *p* = 0.026 at 8 w, n.s. at 6 m (b) *60% vs. 28% (PTSD vs. no PTSD), p = 0.028*
Weinert et al. (*n* = 149)[41]	*T*-tests or ANOVA or Nonparametric tests	(a) Delirious vs. no delirious memories (b) Female sex	(a) Mean PTSD-like severity score: 7 (8) vs. 5 (6), *p* = 0.018 at 2 m PTSD diagnosis: 19% vs. 14%, n.s. (b) OR 2.2 (0.9-5.2), n.s.
Jones et al. (*n* = 238)[42]	Spearman's correlation	(a) Previous psychiatric history (b) Amount of sedation in ICU (c) Amount of opiates in ICU (d) Physical restraint in ICU (e) Mean hours restrained in ICU (f) "Delusional memories" of ICU 2 w post-ICU	(a) *rho* = 0.23, *p* = 0.0003 (b) *rho* = 0.15, *p* = 0.02 (c) *rho* = 0.28, *p* < 0.0001 (d) *rho* = 0.33, *p* < 0.0001 (e) *rho* = 0.19, *p* = 0.003 (f) *rho* = 0.23, *p* = 0.0003

Study (n)	Measure of association	Potential risk/protective factor	Outcome: post-traumatic stress symptoms/disorder
Cuthbertson et al. (*n* = 78)[43]	χ2 or Spearman's correlation	(a) Admission diagnosis; patient concern regarding severity/likelihood of death from critical illness/injury; sex; ICU LOS; APACHE II score	(a) n.s.
	Mann-Whitney *U*	(b) Age	(b) *49 vs. 62 yrs (PTSD vs. no PTSD), p* = 0.04
	Spearman's correlation	(c) Saw physician for mental health pre-ICU	(c) *p* = 0.005
		(d) Days of MV	(d) *p* = 0.01
Costa et al. (*n* = 90)[45]	Fisher's exact test		**Comparisons: PTSD vs. no PTSD**
		(a) Male	(a) *55% vs. 71%, p = 0.15*
		(b) Age ≤ 50 yrs	(b) *95% vs. 75%, p = 0.05*
		(c) Cause of admission	(c) *p = 0.54*
		(d) Time in the ICU	(d) *p = 1.00*
		(e) Sedation received in the ICU	(e) *65% vs. 67%, p = 0.82*
		(f) Duration of sedation	(f) *p = 0.68*
		(g) Level of sedation	(g) *p = 0.34*
		(h) ICU memories	(h) *80% vs. 75%, p = 0.72*
		(i) Type of memories	(i) *p = 0.44*
		(i.1) No memory	(i.1) *20% vs. 24%*
		(i.2) Factual memories	(i.2) *30% vs. 43%*
		(i.3) Illusive memories	(i.3) *0.0% vs. 3%*
		(i.4) Factual and illusive memories	(i.4) *50% vs. 30%*
		(j) Duration of MV	(j) *p = 0.50*
Schandl et al. (*n* = 30)[46]	Repeated measures ANOVA or Friedman test or Student's *T*-test or Pearson's χ^2 test or Mann-Whitney *U*	(a) Age	(a) Mean age: 46 (17) vs. 57 (18) yrs (IES > 25 vs. IES ≤ 25), *p* = 0.026
		(b) APACHE II score, Trauma, Gender, ICU LOS, Charlson Comorbidity Index	(b) n.s.
Sukantarat et al. (*n* = 51)[47]	Spearman's correlation	Age, ICU LOS, APACHE II score, TISS points	n.s.

Study (n)	Measure of association	Potential risk/protective factor	Outcome: post-traumatic stress symptoms/disorder
Jackson et al. (n = 80)[21]	Mann-Whitney *U*	Spontaneous awakening trial	p = 0.83, at 3 m p = 0.60, at 12 m
Granja (n = 299)[48]	Logistic regression or Kruskal-Wallis	(a) Age, Sex, Employment status, Previous health status, SAPS II, ICU LOS, Diagnostic category (b) ICU memory tool (b.1) Not remembering the hospital stay before ICU admission (b.2) Intrusive memory from hospital stay (b.3) Delusional & Factual memories	(a) n.s. (b.1) OR 2.59 (CI - 1.22 to 5.47) (b.2) OR 3.83 (CI - 1.80 to 8.16) (b.3) Median PTSS-14: *37 (21-51) vs. 27 (18-38), p* = 0.007 (delusional & factual memories vs. delusional & no factual memories)
Cuthbertson et al. (n =213) (PRaCTICal study)[20]	Analysis of covariance	Nurse led follow up clinic	Mean DTS-I at 6 m: 16 (16)[a] vs. 19 (17)[b], p = 0.07 Mean DTS-I at 12 m: 12 (14)[a] vs. 15 (16)[b], p = 0.05 Mean DTS-S at 6 m: 14 (14)[a] vs. 17 (15)[b], p = 0.10 Mean DTS-S at 12 m: 10 (14)[a] vs. 12 (13)[b], p = 0.37
Garrouste-Orgeas et al. (n = 56)[14]	Kruskal-Wallis or χ^2 test or Logistic and linear regressions	(a) ICU diary (b) IES-R scores in relatives (c) Gender (female) (d) Age (e) Antidepressant in past 3 m (f) Anxiolytic in past 3 m (g) Previous psychiatric admission (h) Previous psychiatric outpatient care (i) ICU LOS, Post-ICU hospital LOS, SAPS II, Logistic organ failure, Type of patient, Reason for admission (j) ICU care (j.1) Endotracheal tube (j.2) Epinephrine/norepinephrine	**Comparisons: PTSD vs. no PTSD** (a) Mean IES-R: 21 (12)[a] vs. 32 (15)[b], *p = 0.004* *PTSD prevalence: 50%[a] vs. 69%[b], n.s.* (b) *rho = 0.3, p = 0.02* (c) *54% vs. 19%, p = 0.01* (d) *p = 0.4* (e) *14% vs. 5%, p = 0.4* (f) *23% vs. 9%, p = 0.2* (g) *9% vs. 9%, p = 0.2* (h) *14% vs. 9%, p = 0.7* (i) *n.s.* (j.1) *77% vs. 48%, p = 0.016* (j.2) *40% vs. 43%, p = 1.00*

Study (n)	Measure of association	Potential risk factor	Outcome: post-traumatic stress symptoms/disorder
		(j.3) Dobutamine (j.4) Dialysis (j.5) Central venous catheter (j.6) Arterial catheter (k) ICU stay events (l) ICU stay treatment (l.1) Corticosteroids (l.2) Benzodiazepines (l.3) Morphine (l.4) Neuromuscular blockers (m) Peritraumatic dissociation score (3 m post-d/c)	(j.3) *11% vs. 0%, p = 0.3* (j.4) *14% vs. 9%, p = 0.7* (j.5) *63% vs. 48%, p = 0.3* (j.6) *40% vs. 38%, p = 1.00* (k) *20% vs. 19%, p = 1.00* (l.1) *49% vs. 33%, p = 0.2* (l.2) *66% vs. 38%, p = 0.051* (l.3) *74% vs. 52%, p = 0.12* (l.4) *49% vs. 24%, p = 0.09* (m) *p = 0.11*
Badia-Castelló et al. (*n* = 169)[49]	One-way ANOVA or χ^2 test	(a) Female vs. male (b) No memory vs. without illusion memories vs. with illusion memories	(a) Mean IES: 11 (14) vs. 4 (6), no *p*-value (b) Mean IES: 1 (6) vs. 6 (8) vs. 11 (12), $p < 0.001$
Scragg et al. (*n* = 77)[24]	Pearson's correlation and regression	Age, ICU LOS, Time since ICU discharge	n.s.
Schandl (*n* = 171)[32]	Man-Whitney *U* or Logistic quantile regression	(a) Females vs. males (b) Females in ICU follow up vs. control (c) Males in ICU follow up vs. control (d) Males (e) Psychiatrist evaluation and treatment (e.1) Females (e.2) Males	(a) *Median IES: 24.5 vs. 13, p < 0.01*[c] (b) *Median IES: 20*[a] *vs. 31*[b]*, p = 0.01* (c) *Median IES: 16*[a] *vs. 10*[b]*, p = 0.27* (d) n.s. (e.1) *Median IES n = 6, 35 vs. 21 (3 m vs. 14 m), p < 0.05* (e.2) *Median IES n = 3, 28 vs. 10 (3 m vs. 14 m), p = 1.0*
Richter et al. (*n* = 37)[50]	*T*-test or Mann-Whitney *U*	(a) Age, APACHE II score, Injury severity score, ICU LOS, Time until follow up, Duration of ventilation, Duration of sedation, Traumatic brain injury, Previous psychiatric disorder (b) Additional psychiatric diagnoses at follow-up	(a) n.s. (b) *86% vs. 11%, p = 0.004 (PTSD vs. no PTSD)*

Study (n)	Measure of association	Potential risk factor	Outcome: post-traumatic stress symptoms/disorder
Bugedo et al. (*n* = 75)[31]	Fisher's exact test Student's t-test Mann-Whitney-Wilcoxon test	(a) recall of traumatic memories (b) benzodiazepine use and dose (c) analgesia use and dose (d) NMB use and dose (e) level of sedation during mechanical ventilation (f) Analgesia-based sedation protocol	(a) $p<0.005$ (b) n.s. (c) n.s. (d) n.s. (e) n.s. (f) n.s.
Paparrigopoulos et al. (*n* = 48)[26]	Spearman's correlation coefficients One-way ANOVA χ^2 test Multivariable linear and logistic regression	(a) traumatic events during adulthood (b) previous psychiatric history (c) stressful life events (d) CES-D scores (e) sex (f) age (g) childhood traumatic events (h) social issues	(a) r=0.439, p=0.002; β=17.01, p=0.037; x^2=3.692, p=0.055; OR=2.819, p=0.093 (b) r=0.439, p=0.002; β=19.76, p=0.003; x^2=11.429, p=0.001; OR=13.01, p=0.003 (c) r=0.337, p=0.005; x^2=5.333, p=0.023; OR=3.353, p=0.067 (d) r=0.714, $p<0.001$ (e) ns (f) n.s. (g) n.s. (h) n.s.
Davydow et al. (*n* = 80)[29]	Mixed-model linear regression analyses	a) CRHBP A/T b) CRHBP T/T c) CRHR1 C/T d) CRHR1 C/C e) age f) non-white g) SAPS II h) in-ICU corticosteroid exposure	a) β=-1,6 (-5.8, 2.6), p=0.44 b) β=-11.1 (-17.8, -4.7), p=0.002 c) β=4.0 (-8.4, 16.3), p=0.53 d) β=0.2 (-12.3, 11.9), p=0.98 e) β=-0.1 (-0.3, 0.02), p=0.09 f) β=6.4 (1.6, 11.1), p=0.009 g) β=n.s. h) β=n.s.

Study (n)	Measure of association	Potential risk factor	Outcome: post-traumatic stress symptoms/disorder
Davydow et al. (*n* = 131)[30]	Mixed-model linear regression analysis	(a) in-hospital substantial acute stress symptoms (b) number of prior traumatic event exposures (c) age (d) sex (e) race (f) education (g) marital status (h) lifetime history of major depression (i) alcohol use (j) drug abuse (k) associated comorbidities (l) mechanically ventilated (m) required major surgery (n) required blood product transfusion (o) in-hospital probable delirium (p) days of exposure to hospital exposure to BZD, opioids, antipsychotics, antidepressants (q) required physical restraints	(a) β=17.3(95% CI: 12.1-22.4); $p<0.001$[d] β=16.9(95% CI: 11.4-22.4); $p<0.001$[e] (b) n.s. (c) n.s. (d) n.s. (e)n.s. (f) n.s. (g) n.s. (h) n.s. (i) n.s. (j) n.s. (k) n.s (l) n.s. (m) n.s. (n) n.s. (o) n.s. (p) n.s. (q)n.s.
Azoulay et al. (*n*=154)[28]	Wilcoxon rank-sum test Pearson Chi Square Test Fishers exact test	No treatment-limitation decisions versus do-not-intubate order	$p=0.13$
Wade et al. (*n* = 100)[27]	Pearson's correlation, Spearman's correlation, t-tests, one-way ANOVA,	(a) length of stay in ICU (b) length of hospital stay (c) type of admission (d) post hospital destination (e) primary body system (f) use of opiods	(a) n.s. (b) n.s. (c) n.s. (d) n.s. (e) n.s. (f) n.s

Study (n)	Measure of association	Potential risk factor	Outcome: post-traumatic stress symptoms/disorder
	Multivariable regression analysis	(g) use of steroids (h) age (i) sex (female vs male) (j) ethnicity (white vs other) (k) socio-economic position (l) duration of sedation (days) (m) benzodiazepines (yes/no) (n) antipsychotics (yes/no) (o) ICU Mood (p) ICU intrusive memories (q) psychological history (yes/no) (r) Alcohol use (yes/no) (s) Brief Illness Perception Questionnaire	(g) n.s. (h) n.s. (i) n.s. (j) n.s. (k) n.s. (l) β=0.33 (-0.18, 0.84) (m) β=0.352, *p*=0.87 (n) β=1.06, *p*=0.62 (o) β=0.25, *p*<0.01 (p) β=5.83,*p*<0.01 (q) β=6.55, *p*<0.05 (r) β=4.63, *p*=0.14 (s) β=0.71, *p*=0.05
Van Ness et al. (*n* = 152)[52]	Kendall tau_b correlation matrix	(a) ADL disability post-ICU (b) cognitive impairment post-ICU (c) delirium post-ICU (d) depression post-ICU	(a) tau_b (standard error) = 0.20 (0.05), p<0.05 (b) tau_b (standard error) = 0.18 (0.10), p>0.05 (c) tau_b (standard error) = 0.11 (0.11), p>0.05 (d) tau_b (standard error) = 0.26 (0.06), p<0.05
Strom et al. (*n* = 26)[18]	Two-sample *T* Test, χ^2 test	Sedation vs. no sedation	PTSS-10 score > 35: 1(8%)[a] vs. 0 (0)[b], *p* = 0.14 Median (IQR) PTSS-10 score: 3 (0-6.5)[a] vs. 10 (6-17)[b], *p*=0.09 IES-R score > 32: 1(8%)[a] vs. 2 (15%)[b], *p*=0.50 Median (IQR) IES-R score: 4 (2-8)[a] vs. 2 (0-11)[b], *p*=0.41
Sackey et al. (*n* = 17)[17]	Spearman's Correlation Fisher's exact test	(a) isoflurane sedation vs. Midazolam sedation (b) number of encircled memories of feelings (c) memories of negative feelings from ICU (d) memories of delusions from ICU (e) "real" memories from ICU (f) previous posttraumatic experiences	(a) *n.s.* (b) *rho*=.82, *p*=.001 (c) moderate or high IES scores, *p*=0.01 (d) n.s.

Study (n)	Measure of association	Potential risk factor	Outcome: post-traumatic stress symptoms/disorder
			(e) n.s. (f) n.s.
Nickel et al. (*n* = 41)[25]	Fischer's exact test Mann-Whitney U	(a) prior psychiatric disease (b) APACHE II	(a) PTSD vs no-PTSD, *p*=0.025 (b) *n.s.*
Jones et al. (*n* = 45)[53]	Kruskal wallis test Student's t test Spearman's correlation	(a) diagnostic group (b) premorbid psychopathology (c) no factual memories and delusions vs. no delusional memories at 2 weeks (d) anxiety at 2 weeks (e) anxiety at 8 weeks (g) State-Trait anxiety inventory score	(a) n.s. (b) n.s. (c) *p*<0.05 (d) *rho*=0.45, *p*=0.014 (e) *rho* = 0.39, *p*=0.035 (g) *rho* = 0.30, *p*=0.108
Girard et al. (*n* = 43)[54]	Multiple linear regression Spearman's correlation Wilcoxon rank-sum test	(a) total dose of lorazepam (b) female vs. male gender (c) duration of delirium (d) APACHE II score (e) duration of mechanical ventilation (f) ICU LOS (g) Memories of traumatic ICU experiences (h) Composite neuropsychological test scores (i) age	(a) β=0.39 for 10mg increase in lorazepam, *p*=0.001 (b) β=7.36, *p*=0.02; median (IQR) PTSS-10 score 22(16-35) vs, 17(12-27), *p*=0.06 (c) n.s. (d) n.s. (e) *rho*=0.034, *p*=0.83 (f) *rho*=0.10, *p*=0.51 (g) *rho*=0.366, *p*=0.02 (h) *rho*=-0.079, *p*=0.63 (i) *p*=0.04

ADL indicates activities of daily living; ANOVA, analysis of variance; APACHE II, Acute Physiology and Chronic Health Evaluation II Score; β, linear regression coefficient in multivariable model; βst, standardized linear regression coefficient in multivariable model; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; d, day(s); CRHBP, corticotrophin-releasing hormone binding protein; CRHR1, corticotrophin-releasing hormone receptor type 1; DTS-I indicates Davidson Trauma Scale-Incidence subscale; DTS-S indicates Davidson Trauma Scale-Severity subscale; d/c, discharge; "delusional memories," memories of in-ICU psychotic/nightmare experiences; ED, emergency department; GCS, Glasgow Coma Scale; HAD, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; IES-A, Impact of Events Scale-Avoidance Subscale; IES-I, Impact of Events Scale-Intrusion Subscale; IES-R, Impact of Events Scale-Revised; ICU, intensive care unit; LOS, length of stay; m, month(s); MV, mechanical ventilation; MAAS, Motor Activity Assessment Scale; n.s., not significant (no p-value given); NMB,

neuromuscular blockers; OR, odds ratio; P_{75}, 75^{th} Percentile; PTSD, posttraumatic stress disorder; PTSS-14, Post Traumatic Symptom Scale-14; rho, Correlation coefficient; SAPS II, Simplified Acute Physiology Score; SCL 90 R, Symptom Checklist-90-Revised; TISS, Therapeutic Intervention Scoring System; w, week(s); χ2, Chi-square test; yrs, years.

a = Intervention group
b = Control group
c = Values updated after enquiring respective authors
d = adjusted for patient characteristics
e = adjusted for hospitalization characteristics

Table 6. Associations of PTSD symptoms/PTSD diagnosis and Quality of Life

Study (n)	Measure of association	Follow-up in months	Posttraumatic stress symptoms instrument	HRQOL Instrument(s)	Test value(s)
Myhren et al. (*n* = 192)[36]	Multivariable linear regression analyses	12	IES	SF-36 PF SF-36 MH	β = -9.1 (-17.6 to -0.6), *p* < 0.05 (IES ≥20 vs. PF) β = -11.6 (-17.3 to -6.0), *p* < 0.001 (IES ≥ 20 vs. MH)
Sukantarat et al. (*n* = 51)[47]	Spearman's correlation	3 9 IES-I	IES-A IES-I IES-A IES-I	EQ-5D VAS SF-36 PCS SF-36 MCS EQ-5D VAS SF-36 PCS SF-36 MCS EQ-5D VAS SF-36 PCS SF-36 MCS EQ-5D VAS SF-36 PCS SF-36 MCS	*rho* = -0.34, *p* < 0.005 *rho* = -0.28, n.s. *rho* = -0.34, *p* < 0.05 *rho* = -0.24, *p* > 0.05 *rho* = -0.06, n.s. *rho* = -0.38, *p* < 0.05 *rho* = -0.50, *p* < 0.001 *rho* = -0.23, n.s. *rho* = -0.48, *p* < 0.001 *rho* = -0.50, *p* < 0.001 *rho* = -0.16, n.s. *rho* = -0.49, *p* < 0.001
Van Der Schaaf et al. (*n* = 238)[23]	Spearman's correlation	12	IES	SIP 68	*rho* = 0.260, *p* < 0.001
Paparrigopoulos et al. (n = 48)[26]	Spearman's correlation	21(3)	DTS	SF-36 SF-36 MH SF-36 PH	r=-0.291, p < 0.05 r=-0.610, p < 0.001 n.s.
Sackey et al. (n = 28)[17]	Spearman's correlation	17	IES	Well-Being Index	*rho* = -0.67, *p* < 0.005
Girard et al. (n = 43)[54]	Spearman's correlation	6	PTSS-10	SF-12	*rho*=-0.565, *p* < 0.0001

β indicates linear regression coefficient in multivariable model; DTS, Davidson Trauma Scale; EQ-5D VAS, Euro-Quality of life Visual Analogue Scale; IES, Impact of Events Scale; IES-A, Impact of Events Scale–Avoidance Subscale; IES-I, Impact of Events Scale–Intrusion Subscale; n.s., not significant; PTSS-10, Posttraumatic Symptom Scale – 10; rho, Correlation coefficient; SF-12, Short Form-12; SF-36, Short Form-36; SF-36 MCS, Short Form-36 Mental Component Summary; SF-36 MH, Short Form-36 Mental Health; SF-36 PCS, Short Form-36 Physical Component Summary; SF-36 PF, Short Form-36 Physical Functioning; SIP 68, Sickness Impact Profile 68.

The SF-36 and SF-12 have two overall summary measures known as the Mental Component Summary and the Physical Component Summary (norm-based score 0-100, with higher scores indicating better health-related quality of life (HRQOL)). EQ5D – scored 0-100 with higher scores indicating better HRQOL. SIP68 – scored 0-68 with higher scores indicating worse HRQOL. Well-being index – scored 0-30 with higher scores indicating better well-being.

Chapter 4 – Section B Tables

eTable 1. Consolidated Framework for Implementation Research (CFIR) domains and reported constructs as defined in Damschroder et al.*

Domain **Construct**	**Description**
Intervention Characteristics	"Core components of the intervention itself and an adaptable periphery including elements, structures and systems related to the intervention"
• Adaptability	"Degree to which an intervention can be adapted, tailored, refined or reinvented to meet local needs"
• Design Quality	"Perceived excellence in how the intervention is bundled, presented, and assembled"
Outer Setting	"Economic, political, and social context of the organization that an intervention occupies"
• Patient Needs and Resources	"Extent to which patient needs, as well as barriers and facilitators to meet those needs, are accurately known and prioritized by the organization"
Inner Setting	"Economic, political, and social context through which implementation process proceeds"
• Culture	"Norms, values and basic assumptions of a given organization"
• Implementation Climate	"Absorptive capacity for change, shared receptivity of involved individuals to an intervention, and the extent to which use of that intervention with be 'rewarded, supported, and expected within their organization'."
• Relative Priority	"Individuals' shared perception of the importance of the implementation within the organization"
• Structural Characteristics	"Social architecture, age, maturity, and size of an organization"
• Available Resources	"Level of resources dedicated for implementation and ongoing operations including money, training, education, physical space, and time"
Characteristics of Individuals	"Individuals involved with the intervention and/or implementation process"

• Knowledge and Beliefs about Intervention	"Individuals' attitudes toward and value placed on the intervention, as well as familiarity with facts, truths, and principles related to the intervention"
Implementation Process	"Interrelated sub-processes that aim to achieve individual and organizational level use of the intervention as designed"
• Engaging	"Attracting and involving appropriate individuals in the implementation and use of the intervention through a combined strategy of social marketing, education, role modeling, training, and other similar activities"

* Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implementation science : IS 2009;4:50.

eTable 2. Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Criteria		Page
Domain 1: research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	5
2. Credentials	What were the researcher's credentials? *E.g. PhD, MD*	5
3. Occupation	What was their occupation at the time of the study?	5
4. Gender	Was the researcher male or female?	5
5. Experience and training	What experience or training did the researcher have?	5
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	4-5
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	3-4
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, etc*	N/A
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	5
Participant selection		
10. Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	4
11. Method of approach	How were participants approached? e.*g. face-to-face, telephone*	4
12. Sample size	How many participants were in the study?	7
13. Non-participation	How many people refused to participate or dropped out? Reasons?	7
Setting		
14. Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	4-5
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	4
16. Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	7
Data Collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	4

Criteria		Page
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	7
19. Audio/visual recording	Did the research use audio or visual recording to collect data?	5
20. Field notes	Were field notes made during and/or after the interview or focus group?	5
21. Duration	What was the duration of the interviews or focus group?	7
22. Data saturation	Was data saturation discussed?	6
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	11 [ł]
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	6
25. Description of coding tree	Did authors provide a description of the coding tree?	6
26. Derivation of themes	Were themes identified in advance or derived from the data?	5-6
27. Software	What software, if applicable, was used to manage the data?	N/A
28. Participant checking	Did participants provide feedback on the findings?	6, 11
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? *e.g. participant number*	Tables 5 & 6[€]
30. Data and findings consistent	Was there consistency between the data presented and the findings?	6-11
31. Clarity of major themes	Were major themes clearly presented in the findings?	6-11
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	6-11, 11-14

*Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349-57.

[ł] Member checking was performed with nurses who were members of the multidisciplinary QI team

[€] Interviews were not transcribed verbatim. Representative statements were taken from detailed field notes kept during interviews.

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63. Nallamothu BK, Hayward RA, Bates ER. Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies. *Circulation* 2008;118:1294-1303.

64. Dinglas VD, Colantuoni E, Ciesla N, Mendez-Tellez PA, Shanholtz C, Needham DM. Occupational therapy for patients with acute lung injury: factors associated with time to first intervention in the intensive care unit. *Am J Occup Ther* 2013;67:355-362.

65. Balas MC, Burke WJ, Gannon D, Cohen MZ, Colburn L, Bevil C, Franz D, Olsen KM, Ely EW, Vasilevskis EE. Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. *Crit Care Med* 2013;41:S116-127.

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2. Girard TD, Thompson JL, Pandharipande PP, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med 2018;6:213-22.

3. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-62.

4. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009;180:1092-7.

5. Klein Klouwenberg PM, Zaal IJ, Spitoni C, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ 2014;349:g6652.

6. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001;27:1892-900.

7. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. N Engl J Med 2013;369:1306-16.

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12. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46:e825-e73.

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14. Kang J, Lee M, Ko H, et al. Effect of nonpharmacological interventions for the prevention of delirium in the intensive care unit: A systematic review and meta-analysis. J Crit Care 2018;48:372-84.

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18. DiCicco-Bloom B, Crabtree BF. The qualitative research interview. Medical Education 2006;40:314-21.

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23. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703-10.

24. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.

25. Dubb R, Nydahl P, Hermes C, et al. Barriers and Strategies for Early Mobilization of Patients in Intensive Care Units. Ann Am Thorac Soc 2016;13:724-30.

26. Devlin JW, Fong JJ, Howard EP, et al. Assessment of delirium in the intensive care unit: nursing practices and perceptions. Am J Crit Care 2008;17:555-65; quiz 66.

27. Hager DN, Dinglas VD, Subhas S, et al. Reducing deep sedation and delirium in acute lung injury patients: a quality improvement project. Crit Care Med 2013;41:1435-42.

28. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. Intensive care medicine 2009;35:1276-80.

29. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669-76.

30. Young DL, Seltzer J, Glover M, et al. Identifying Barriers to Nurse-Facilitated Patient Mobility in the Intensive Care Unit. Am J Crit Care 2018;27:186-93.

31. Hopkins RO, Spuhler VJ, Thomsen GE. Transforming ICU culture to facilitate early mobility. Crit Care Clin 2007;23:81-96.

32. Brummel NE, Vasilevskis EE, Han JH, Boehm L, Pun BT, Ely EW. Implementing delirium screening in the ICU: secrets to success. Crit Care Med 2013;41:2196-208.

CURRICULUM VITAE
The Johns Hopkins University School of Medicine

Ann M. Parker, MD 10/22/2019

DEMOGRAPHIC AND PERSONAL INFORMATION

Born January 26, 1982, in Baltimore, MD, USa

Current Appointments

University
2011-2012 Assistant Professor, Department of Medicine, Medical College of Virginia
2016-present Assistant Professor, Department of Medicine, Johns Hopkins University School of Medicine

Hospital
2011-2012 Attending Physician, Virginia Commonwealth University Hospital
2016-present Attending Physician, Johns Hopkins Hospital

Personal Data

Pulmonary, Critical Care & Sleep Medicine
Medicine
1830 Building, 5th Floor
1830 East Monument St.
Baltimore, MD 21205
Tel 410 955 3467
Fax 410 367 2014
E-mail ann.parker@jhmi.edu

Education and Training

Undergraduate
2004 B.A. Franklin and Marshall College, Lancaster, PA; graduated summa cum laude

Doctoral/graduate
2008 M.D., University of Maryland School of Medicine, Baltimore, MD

Postdoctoral
2008-2011 Resident, Medicine, University of Maryland Medical Center, Baltimore, MD
2012-2016 Fellowship, Pulmonary, Critical Care & Sleep Medicine, Dale M. Needham, MD, Johns Hopkins University School of Medicine, Baltimore, MD

Professional Experience

2011-2012	Assistant Professor, Medicine, Virginia Commonwealth University Hospital
2016-2017	Instructor, Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
2017-present	Assistant Professor, Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

PUBLICATIONS

Original Research [OR]

1. **Parker AM**, Liu X, Harris AD, Shanholtz CB, Smith RL, Hess DR, Reynolds M, Netzer G: Respiratory therapy organizational changes are associated with increased respiratory care utilization. Respiratory Care. 2013:58:438-449. PMID: 22782139
2. Verceles AC, Liu X, Terrin ML, Scharf SM, Shanholtz C, Harris A, Ayanleye B, **Parker AM**, Netzer G: Ambient light levels and critical care outcomes. Journal of Critical Care. 2013:28:110 e111-118. PMID: 22762935
3. Sricharoenchai T, **Parker AM,** Zanni JM, Nelliot A, Dinglas VD, Needham DM. Safety of physical therapy interventions in critically ill patients: A single center prospective evaluation of 1,110 ICU admissions. Journal of Critical Care. 2013:29(3): 395-400. PMID: 24508202
4. Dinglas VD*, **Parker AM***, Reddy DR, Colantuoni E, Zanni JM, Turnbull AE, Nelliot A, Ciesla N, Needham DM. A quality improvement project sustainably decreased time to onset of active physical therapy intervention in patients with acute lung injury. Annals of the American Thoracic Society. 2014:11(8):1230-8. PMID: 25167767 Dinglas and Parker were co-first authors with equal contribution to the research.
5. **Parker AM**, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic Stress Disorder in Critical Illness Survivors: A Metaanalysis. Critical Care Medicine. 2015: 43(5): 1121-9. PMID: 25654178 [Press release at the American Thoracic Society Conference 2015]
6. Eakin MN, Ugbah L, Arnautovic T**, Parker AM**, Needham DM. Implementing and Sustaining an Early Rehabilitation Program in a Medical Intensive Care Unit: A Qualitative Analysis. Journal of Critical Care. 2015:30(4):698-704. PMID: 25837800.
7. Huang M, **Parker AM**, Bienvenu OJ, Dinglas VD, Colantuoni E, Hopkins, RO, Needham DM; with the National Institutes of Health, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Psychiatric symptoms in acute respiratory distress syndrome survivors: A 1-year national multicenter study. Critical Care Medicine. 2016: 44(5): 954-65. PMID: 26807686
8. Hodgson CL, Turnbull AE, Iwashyna TJ, **Parker AM**, Davis W, Bingham CO, Watts N, Finfer S, Needham DM. Clinician and researcher perspectives on core domains in evaluating post-discharge patient outcomes after acute respiratory failure. Physical Therapy Journal. 2017: 97(2): 168-174. PMID: 28204767
9. Dinglas VD, Chessare CM, Davis WE, **Parker A**, Friedman LA, Colantuoni E, Bingham CO, Turnbull AE, Needham DM. Perspectives of survivors, families, and researchers on key outcomes for research in acute respiratory failure. *Thorax*. 2017:73(1):7-12. PMID: 28756400
10. Young DL, Seltzer J, Glover M, Outten C, Lavezza A, Mantheiy E, **Parker AM**, Needham DM. Identifying Barriers for Nurse-Facilitated Patient Mobility in the Intensive Care Unit. Am J Crit Care. 2018; In press.
11. Goodson CM, Friedman LA, Mantheiy E, Heckle K, Lavezza A, Toonstra A, **Parker AM**, Seltzer J, Velaetis M, Glover M, Outten C, Schwartz K, Jones A, Coggins S, Hoyer EH, Chan KS, Needham

DM. Perceived Barriers to Mobility in a Medical ICU: The Patient Mobilization Attitudes & Beliefs Survey for the ICU. *J Intensive Care Med.* 2018 (online)

12. Hosey MM, Leoutsakos JM, Li X, Dinglas VD, Bienvenu JO, **Parker AM**, Hopkins RO, Needham DM, Neufeld KJ. Screening for posttraumatic stress disorder in ARDS survivors validation of the impact of event scale-6 (IES-6). *Critical Care.* 2019; In press

Review Articles [RA]

1. **Parker A**, Sricharoenchai T, Needham DM. Early rehabilitation in the intensive care unit: preventing physical and mental health impairments. Current Physical Medicine and Rehabilitation Reports. 2013:1(4):307-314. PMID: 24436844. PMCID: PMC3889146
2. **Parker A**, Needham DM. The importance of early rehabilitation and mobility in the ICU. Critical Connections. 2013: 12(4): 8-9.
3. **Parker A**, Needham DM. Rehabilitation: prevention and management of neuromuscular weakness in the intensive care unit. In Acquired Neuromuscular Weakness in Critical Illness. American Association of Neuromuscular and Electrodiagnostic Medicine 2013.
4. Karnatovskaia LV, Philbrick KL, **Parker AM,** Needham DM. Early psychological therapy in critical illness. Seminars in Respiratory and Critical Care Medicine. 2016:37(1): 136-42. PMID:26820280.
5. Dubb R, Nydahl P, Hermes C, Schwabbauer N, Toonstra A, **Parker AM**, Kaltwasser A, Needham DM. Barriers and strategies for early mobilization of patients in intensive care units. Annals of the American Thoracic Society. 2016:13(5): 724-30. PMID:268295
6. Hashem MD, **Parker AM**, Needham DM. Early mobilization and rehabilitation of the critically ill patient. Chest. 2016: 150(3):722-31. PMID:26997241

Other Publications

Editorials [ED]

1. **Parker A**, Tehranchi KM, Needham DM. Critical care rehabilitation trials: the importance of 'usual care'. Critical Care. 2013: 17(5): 183. PMID:24103735. PMCID:PMC4056109
2. **Parker AM**, Lord RK, Needham DM. Increasing the dose of acute rehabilitation: is there a benefit? BioMed Central Medicine. 2013:11:199. PMID:24228867. PMCID:PMC3844507
3. Lambert A, **Parker AM**, Moon K. High-dose N-acetylcysteine in chronic obstructive pulmonary disease, prone positioning in acute respiratory distress syndrome and continuous positive airway pressure and exhaled nitric oxide in obstructive sleep apnea. American Journal of Respiratory and Critical Care Medicine. 2014:189(2):223-4. PMID:24428648. PMCID:PMC3983893
4. Turnbull AE, **Parker AM**, Needham DM. Supporting small steps toward big innovations: the importance of rigorous pilot studies in critical care. Journal of Critical Care, 2014, 29(4):669-70. PMID 24930365.
5. **Parker AM**, Bienvenu OJ. Posttraumatic stress disorder symptoms among family decision makers and the potential relevance of study attrition. Critical Care Medicine. 2015:43(6):1334-5.
6. **Parker AM**, Nikayin S, Bienvenu OJ, Needham DM. Validity of the Posttraumatic Stress Symptoms-14 Instrument in Acute Respiratory Failure Survivors. Annals of the American Thoracic Society. 2017: Epub ahead of print. PMID 28355099
7. Alugubelli NR, Al-Ani A, Needham DM, **Parker AM**. Understanding early goal-directed mobilization in the surgical intensive care unit. Annals of Translational Medicine. 2017: 5(7):176. PMID 28480212

8. **Parker AM**, Malik A, Hosey M. Process evaluation and the development of behavioural interventions to improve psychological distress among survivors of critical illness. *Thorax.* 2018; epub.

Media Releases or Interviews [MR]

5/19/14 American Thoracic Society Press Conference, Critical Care, moderated by Greg Martin, MD, "A Meta-Analysis Of Post-Traumatic Stress Disorder (PTSD) Symptoms In Intensive Care Unit Survivors", video interview included

7/27/14 Interviewed by Reporter Laura Benshoff on radio WHYY "The Pulse", "Around one-third ICU survivors get PTSD, but diaries offer hope for recovery," Original 6 min interview at 10 am; article on website http://www.newsworks.org/index.php/local/item/70703-around-one-third-icu-survivors-get-ptsd-but-diaries-offer-hope-for-recovery

4/21/15 Interviewed by Reporter on television WJLA, Washington, DC (ABC news affiliate). "PTSD in ICU survivors," Original 6 min interview at 4pm.

FUNDING

EXTRAMURAL Funding

Research Extramural Funding - Current

09/17 – current Loan Repayment Program
NIH/NHLBI
PI: Parker AP

09/17 – current K23HL138206
NHLBI
A pilot, feasibility randomized controlled trial of a behavioral activation and rehabilitation intervention to improve psychological and physical impairments in acute respiratory failure survivors
PI: Parker AP

Research Extramural Funding – Previous

7/14-08/17 Loan Repayment Program
NIH/NHLBI
PI: Parker AP
Role: Proposal includes evaluation of posttraumatic stress disorder among ICU survivors

10/13-8/17 Institute for Clinical and Translational Research
4KL2TR001077-01
NIH/NCATS
$2,219,191
PI: Ford, DE

Role: Awardee, Clinical Research Scholar, 80%; My project focuses on Posttraumatic stress disorder in survivors of critical illness

Educational Extramural Funding – Previous

7/12-10/13 Multidisciplinary Training Program in Lung Disease
5T32HL007534
NIH/NHLBI
PI: Wise R
Role: postdoctoral fellow

7/14-6/15 Multidisciplinary Training Program in Lung Disease
5T32HL007534
NIH/NHLBI
PI: Wise R
Role: postdoctoral fellow

CLINICAL ACTIVITIES

Clinical Focus – Pulmonary and Critical Care Medicine

Certification

Medical, other state/government licensure

5/11-1/14 Virginia Board of Medicine (#0101249747); expired
6/16-present Maryland Board of Physicians (D81995); active

Boards, other specialty certification

2011-present Board Certified, American Board of Internal Medicine
2017-present Board Certified, Pulmonary disease, American Board of Internal Medicine
2018-present Board Certified, Critical Care Medicine, American Board of Internal Medicine

Clinical (Service) Responsibilities

2016-present Attending, Pulmonary and Critical Care Medicine, 20% effort

Clinical Demonstration Activities

7/8/16 Instructed a lab on bronchoscopic removal of foreign bodies, Introduction to Bronchoscopy Course, Johns Hopkins University SOM

EDUCATIONAL ACTIVITIES

Teaching

Clinical instruction

JHMI/Regional

2011-2012 Attending, 3rd & 4th year med students/residents; Inpatient Medicine service. 4-6 weeks each year, Virginia Commonwealth University

2016-present Attending, fellows; Oncology ICU. 8 weeks each year, Johns Hopkins SOM

CME instruction

JHMI/Regional

9/15 Lecturer, "A zebra or a horse: an underrecognized syndrome in the intensive care unit," Pulmonary and Critical Care Medicine Grand Rounds, Johns Hopkins Hospital

10/15 Lecturer, "Alpha-1 Antitrypsin deficiency: Is Augmentation therapy efficacious?," Pulmonary and Critical Care Medicine Grand Rounds, Johns Hopkins Hospital

3/16 Lecturer, "Experience with proning in the JHH MICU," Pulmonary and Critical Care Medicine Grand Rounds, Johns Hopkins Hospital

6/16 Lecturer, "The sun should never set on a parapneumonic effusion," Pulmonary and Critical Care Medicine Grand Rounds, Johns Hopkins Hospital

12/16 Lecturer, "Discussing prognosis with intensive care unit surrogates: dealing with uncertainty," Pulmonary and Critical Care Medicine Grand Rounds, Johns Hopkins Hopsital

Mentoring

Post-doctoral Advisees /Mentees

7/1/16 – present Ishani De, MD, Post-doctoral research fellow, Outcomes After Critical Illness and Surgery research group, Johns Hopkins University

9/1/16 – present Awsse Al-Ani, MD, Post-doctoral research fellow, Outcomes After Critical Illness and Surgery research group, Johns Hopkins University

9/1/16 – present Navya Alugubelli, MD, Post-doctoral research fellow, Outcomes After Critical Illness and Surgery research group, Johns Hopkins University

9/1/17 – present Albahi Malik, MD, Post-doctoral research fellow, Outcomes After Critical Illness and Surgery research group, Johns Hopkins University

RESEARCH ACTIVITIES

Research Focus

- post-intensive care syndrome
- behavioral interventions to improve mental health impairments in survivors of critical illness
- impairments in physical function in survivors of critical illness

SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES

12/1/16 – present Faculty advisor, Activity and Mobility Promotion Quality Improvement Project, Medical Intensive Care Unit, Johns Hopkins Hospital

ORGANIZATIONAL ACTIVITIES

Institutional Administrative Appointments

2016-present Member, Lung Research Conference Committee, Pulmonary and Critical Care Medicine
2018-present Member, Clinical Fellows Review Committee, Pulmonary and Critical Care Medicine
2019-present Member, Research Fellows Review Committee, Pulmonary and Critical Care Medicine
2019-present Member, Mortality Review Committee, Pulmonary and Critical Care Medicine

Journal peer review activities

2014 *BMC Medicine*
2014 *Critical Care*
2014 *Critical Care Medicine*
2016 *BMJ Open*
2018 *Thorax*
2018 *JAMA*

Professional Societies

2004-present Phi Beta Kappa Honor Society
2008-present Member, Alpha Omega Alpha (AOA)
2011-present Member, American Thoracic Society (ATS)
2012-present Member, Society of Critical Care Medicine (SCCM)
2012-2014 Physician Liaison, American Association for Respiratory Care, Maryland/District of Columbia Regional Chapter

RECOGNITION

Awards, Honors

2003 Isaac E. Roberts Prize in Biology, Franklin and Marshall College
2003 Alpha Epsilon Delta National Premed Honor Society, Franklin and Marshall College
2004 Charles N. Stewart Award in Neuroscience, Fredrick C. Schiffman Pre-Healing Arts Award, Margaret R. Eyler M.D. Healing Arts Award, Franklin and Marshall College
2000-2004 Presidential Scholarship Recipient, Franklin and Marshall College
2004 Phi Beta Kappa Honor Society, Franklin and Marshall College
2006-2007 Baltimore City Medical Society Scholarship Recipient, University of Maryland
2008 Alpha Omega Alpha (AOA), University of Maryland School of Medicine
2008 Humanism Honor Society, University of Maryland School of Medicine
2012 Physician Excellence Award, American Association for Respiratory Care, Maryland/District of Columbia Regional Chapter 2013 American Thoracic Society Abstract Scholarship

Invited Talks

JHMI/Regional

2012 Speaker, MD/DC Society for Respiratory Care Annual Symposium, "Paradigm Shifts in Respiratory Therapy: Changing Roles and Staffing Needs," Ocean City, MD

2016 Speaker, Fifth Annual Johns Hopkins Critical Care Rehabilitation Conference, "ICUAW & Long-Term Physical Outcomes," Baltimore, MD

2017 Speaker, Sicth Annual Johns Hopkins Critical Care Rehabilitation Conference, "ICUAW & Long-Term Physical Outcomes," Baltimore, MD

2018 Speaker, Internal Medicine Grand Rounds, "Post-Intensive Care Syndrome", Rutgers University, Newark, NJ

2018 Speaker, Seventh Annual Johns Hopkins Critical Care Rehabilitation Conference, "ICUAW & Long-Term Physical Outcomes," Baltimore, MD

2018 Speaker, Seventh Annual Johns Hopkins Critical Care Rehabilitation Conference, "The Evidence for Early Rehabilitation in the ICU", Baltimore, MD

2018 Speaker, "Post-Intensive Care Syndrome (PICS): Understanding long-term complications after ICU", University of Maryland School of Medicine, Baltimore, MD

2019 Speaker, New Jersey Regional American Thoracic Society Annual Conference, "Post-Intensive Care Syndrome", New Jersey

2019 Speaker, Eighth Annual Johns Hopkins Critical Care Rehabilitation Conference, "ICUAW & Long-Term Physical Outcomes," Baltimore, MD

2019 Speaker, Eighth Annual Johns Hopkins Critical Care Rehabilitation Conference, "The Evidence for Early Rehabilitation in the ICU", Baltimore, MD

2019 Speaker, Eighth Annual Johns Hopkins Critical Care Rehabilitation Conference, "Critical Care Medications", Baltimore, MD

2019 Speaker, Eighth Annual Johns Hopkins Critical Care Rehabilitation Conference, "Rehabilitation Psychology: Preventing and Treating Mental Health Complications Post-ICU", Baltimore, MD

2019 Speaker, Delirium Consortium Monthly Meeting, "An Occupational Therapy Intervention to Prevent Delirium in Older Critically Ill Adults", Johns Hopkins University School of Medicine, Baltimore, MD

2019 Speaker, The Society of Thoracic Surgeons 16th Annual Multidisciplinary Cardiovascular and Thoracic Critical Care Conference, "ICU Survivorship: I'm 'Recovered'….Not What?", Marriott Waterfront, Baltimore, MD

International

2016 Speaker, 1st World Sepsis Conference, "ICU-Related Posttraumatic Stress Disorders: Treatment & Prevention," Tele-Conference

2019 Speaker, Care of the Psychiatric Patient in the ICU: the First 48 Hours, "Management of Delirium in the ICU", Clinica Alemana, Santiago de Chile

2019 Speaker, Care of the Psychiatric Patient in the ICU: the First 48 Hours, "Delirium in Critical Care: Vision of the Intensivist", Clinica Alemana, Santiago de Chile

2019 Speaker, Care of the Psychiatric Patient in the ICU: the First 48 Hours, "Prevention of Late Psychological Complications of Critical Care", Clinica Alemana, Santiago de Chile

OTHER PROFESSIONAL ACCOMPLISHMENTS

Posters

2009 **Parker A**, Cina M. "Cryptococcal Meningitis in an Immunocompetent Patient. Poster Presentation", American College of Physicians Meeting, Baltimore, MD

2013 **Parker** A, Gellar J, Ruhl AP, Bienvenu OJ, Needham DM. "Post-Traumatic Stress Disorder Risk Factors in Acute Lung Injury Survivors". American Thoracic Society Annual Conference, Philadelphia, PA

2014 Sricharoenchai T*, **Parker AM*,** Raparla S, Schneck K, Bienvenu OJ, Needham DM. "A Meta-Analysis of Post-Traumatic Stress Disorder (PTSD) Symptoms in Intensive Care Unit Survivors." Annual Meeting of the Association for Clinical and Translational Science, Washington, DC.

2014 Sricharoenchai T*, **Parker AM***, Raparla S, Schneck K, Bienvenu OJ, Needham DM. "A Meta-Analysis of Post-Traumatic Stress Disorder (PTSD) Symptoms in Intensive Care Unit Survivors." American Thoracic Society Annual Conference, San Diego, CA.

Oral/Podium Presentations

11/10 **Parker A**, Liu X, Harris A, Smith R, Reynolds M, Shanholtz C, Netzer G. Respiratory Therapy Organization Changes are Associated with Increased Utilization of Best Practice. American College of Chest Physicians Annual Conference, Vancouver, BC.